SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panadol Ultra

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol Ph Eur 500 mg, Codeine phosphate hemihydrate Ph Eur
12.8 mg
Excipients: contains lactose.
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol, aspirin or ibuprofen (alone).

Panadol Ultra Tablets are recommended for the relief of migraine, headache, dental pain, period pain, backache, arthritic & rheumatic pain, strains & sprains and sciatica.

4.2. Posology and Method of Administration

Adults aged 18 years and over (including the elderly)

Two tablets up to 4 times a day. This dose should not be repeated more frequently than every 4 hours, and not more than 4 doses should be given in any 24 hour period. Do not take for more than 3 days without consulting a doctor.

Children aged 16 to 18 years

Two tablets up to 4 times a day. This dose should not be repeated more frequently than every 6 hours, and not more than 4 doses should be given in

any 24 hour period. Do not take for more than 3 days without consulting a doctor.

Children aged 12 to15 years

One tablet up to four times a day. This dose should not be repeated more frequently than every 6 hours, and not more than 4 doses should be given in any 24 hour period. Do not take for longer than 3 days without consulting a doctor.

Children (under12 years)

Not recommended for children under 12 years of age. For oral administration

only.

Do not take for more than 3 days continuously without medical review.

4.3 Contraindications

Hypersensitivity to paracetamol, codeine, opioid analgesics or any of the other constituents.

Codeine is contraindicated in all patients under 18 years who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea.

Use of codeine containing products is contraindicated in mothers who are breast feeding.

4.4 Special Warnings and Special Precautions for Use

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
Do not exceed the stated dose.
Patients should be advised to consult their doctor if their headaches become persistent.
Patients should be advised not to take other paracetamol or codeine-containing products concurrently.
If symptoms persist consult your doctor. Keep out of the reach and sight of children.
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.
Not recommended for use in children in whom respiratory function might be compromised as this may worsen the symptoms of morphine toxicity.
The label will state:

Front of pack

- Can cause addiction

- Use for 3 days only

Back of pack

- Panadol Ultra tablets are for the short term treatment of acute moderate pain when other painkillers have not worked. Wait at least four hours after taking any other painkiller before you take this medicine. For: migraine, headache, dental pain, period pain, backache, arthritic & rheumatic pain, strains & sprains and sciatica.
- If you need to take this medicine continuously for more than 3 days you should see
- your doctor or pharmacist
- This medicine contains codeine which can cause addiction if you take continuously for more than 3 days. If you take this medicine for headaches for more than 3 days
- it can make them worse.

The leaflet will state

- Headlines section (to be prominently displayed)
- This medicine is for the short term treatment of acute moderate pain when other painkillers have not worked.
- You should only take this product for a maximum of 3 days at a time. If you need to take it for longer than 3 days you should see your doctor or pharmacist for advice.
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than 3 days it can make them worse.

Section 1: What the medicine is for:

- Panadol Ultra tablets are for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone. They can be used for migraine, headache, dental pain, period pain, strains & sprains, backache, arthritic & rheumatic pain and sciatica.

Section 2: Before taking

- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it
- If you take a painkiller for headaches for more than 3 days it can make them worse.

Section 3: Dosage

- Do not take for more than 3 days. If you need to use this medicine for more than 3 days you must speak to your doctor or pharmacist
- Possible withdrawal effects
- This medicine contains codeine and can cause addiction if you take it continuously for more than 3 days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: Side effects

- Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.mhra.gov.uk/yellowcard; alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday – Friday) or fill in a paper form available from your local pharmacy.

How do I know if I am addicted?

- If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again

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 summarized
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 Europe	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.

This medicine 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

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. 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.

Codeine

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

Codeine potentiates the central depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines.

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

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 of foetal development.

Lactation

Codeine containing products must not be used while breastfeeding (see *Contraindications).*

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 sedation.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When taking this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been taken to treat a medical or dental problem *and*
  - You have taken it according to the information provided with the medicine *and*
  - It was not affecting your ability to drive safely.

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. The frequency of these adverse events is not known (cannot be estimated from available data).

Paracetamol

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome/toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction

*** There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.**

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 disorder	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 the Yellow Card Scheme at:www.mhra.gov.uk/yellowcard.

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Codeine:

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management

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 350mg or a child more than 5mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

Paracetamol:

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

Risk Factors

If the patient

- Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms

Symptoms of paracetamol overdose in the first 24 hours are 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, cerebral oedema and death. 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 arrhythmias and pancreatitis have been reported.

Management

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 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is an analgesic and antipyretic. Codeine phosphate is a central acting weak analgesic and has weak cough suppressant activity. 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 almost completely absorbed from the gastrointestinal 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.

6.1 List of Excipients

Starch, pre-gelatinised povidone
Potassium sorbate maize starch
Talc
Magnesium stearate
Stearic acid microcrystalline cellulose
Croscarmellose sodium
Opadry II Pink 31F24615 containing:
Lactose monohydrate
Hypromellose
Macrogol
Quinoline yellow (E104)
Erythrosine (E127)
Titanium dioxide (E171)

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

None

6.5 Nature and contents of container

PVC aluminium foil µm blisters in outer cartons, containing 6, 10, 12, 16, 20, 24, 30 or 32 tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (UK) Trading Limited
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Brentford
Middlesex
TW8 9GS
United Kingdom

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