Product Summary

1. Trade Name of the Medicinal Product

Propain Caplets

2. Qualitative and Quantitative Composition

Yellow compressed caplets with a scored line on one side, each containing paracetamol BP 400mg, codeine phosphate BP 10mg, diphenhydramine hydrochloride BP 5mg, caffeine anhydrous BP 50mg.

3. Pharmaceutical Form

Tablets

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, ibuprofen or aspirin (alone). An analgesic used in the treatment of headache, migraine, muscular pain, period pain and toothache.

4.2 Posology and method of administration

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

For oral administration

Adults: take 1 or 2 caplets every 4 hours as required, up to a maximum of 10 caplets in 24 hours. The suggested dosage may also be administered to the elderly (in the absence of other contra-indications).
Paediatric population:

Children age 16-18 years: take 1 or 2 caplets every 6 hours as required, up to a maximum of 8 caplets in 24 hours.

Children aged 12 years to 15 years: take 1 caplet every 6 hours when necessary up to a maximum of 4 caplets in 24 hours.

Children aged less than 12 years:

Codeine is contraindicated 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

- Known sensitivity to paracetamol, codeine, diphenhydramine, caffeine or any of the excipients.

  This medicine should not be used in patients suffering from respiratory depression, acute alcoholism, risk of paralytic ileus, raised intracranial pressure, head trauma and acute abdomen.

- 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)

- In women during breastfeeding (see section 4.6).

- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

Should be taken only with caution by asthmatics. This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant agents. Patients should be warned against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

Dosage in excess of those recommended may cause severe liver damage. Care is advised in the administration of paracetamol-containing product to patients with severe renal or severe hepatic impairment and in those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with alcoholic liver disease. Patients suffering from liver or kidney disease should take paracetamol under medical supervision. The dosage in renal impairment must be reduced.

The elderly are more likely to metabolise or eliminate opioid analgesics more slowly than young adults.
Codeine may cause faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction. Dependence can develop with repeated use of codeine and therefore withdrawal symptoms may appear if the product is withdrawn abruptly. Caution is advised when treating patients with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, shock, obstructive bowel disorders, acute abdominal conditions, recent gastrointestinal surgery, gallstones, a history of cardiac arrhythmias or convulsions. Care should be taken with patients with a history of drug abuse or emotional instability.

**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 therapeutic 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:

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>African/Ethiopian</td>
<td>29%</td>
</tr>
<tr>
<td>African American</td>
<td>3.4% to 6.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2% to 2%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6% to 6.5%</td>
</tr>
<tr>
<td>Greek</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hungarian</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northern European</td>
<td>1%-2%</td>
</tr>
</tbody>
</table>

**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 should be warned of the following via the label and leaflet:

- Do not exceed the recommended dose.
- Do not take any other paracetamol-containing products.
- Consult your doctor if no relief is obtained with the recommended dosage.
- Keep out of the sight and reach of children.
- This product contains paracetamol.
- Immediate medical advice should be sought in the event of an overdose even if you feel well due to the risk of severe liver damage.
- Alcoholic drink should be avoided.

The leaflet will state:

Headlines section (to be prominently displayed)

- This medicine can only be used for .......(indications)
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three 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 three 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 three days it can make them worse

Section 1: What the medicine is for

- Succinct description of the indications from 4.1 of the SmPC Section 2: Before taking
- This medicine contains codeine which can cause addiction if you take it continuously for more than three 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 three 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 three days you must speak to your doctor or pharmacist
- This medicine contains codeine and can cause addiction if you take it continuously for more than three 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.yellowcard.gov.uk;
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

The label will state (prominently but not in a box):

Front of Pack
- Can cause addiction
- For three days use only

Back of Pack
- List of indications as agreed in 4.1 of the SmPC
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse

4.5 Interaction with other medicinal products and other forms of interactions

Paracetamol:
The gastro-intestinal absorption of paracetamol may be delayed by drugs such as anticholinergic agents or opioid analgesics which decrease gastric emptying. Colestyramine may reduce the absorption of paracetamol. Metoclopramide and domperidone may potentiate the speed of absorption of paracetamol.

The likelihood of toxicity may be increased by the concomitant use of enzyme-inducing agents such as alcohol, anti-epileptics, barbiturates and tricyclic antidepressants.

Repeated doses of paracetamol increase the anticoagulant response to coumarins.

Paracetamol with aspirin has been noted to increase the blood concentration of unhydrolysed aspirin.

Diphenhydramine hydrochloride:
The antihistamines can enhance the sedative effect of central nervous system depressants, including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquilisers. The effects of the anticholinergic drugs such as atropine and tricyclic antidepressants may be enhanced. MAOI's may enhance the antimuscarinic effects of antihistamines.

**Caffeine:**
Caffeine enhances the action of the ergot alkaloids in the treatment of migraine. Small doses of caffeine (5 to 10mg/kg) also appear to reduce the ED 50 for aspirin, indometacin and phenylbutazone by more than threefold.

**Codeine Phosphate:**
The depressant effects of some of the opioids may be exaggerated and prolonged by phenothiazines, monoamine oxidase inhibitors and tricyclic antidepressants. Codeine may cause a hypotensive or hypertensive effect if used with MAOI’s. Concomitant use should be avoided and codeine should not be administered until 2 weeks after MAOI’s are discontinued.

Alcohol, antipsychotics, anxiolytics and hypnotics may enhance the sedative and hypotensive effects of codeine.

When codeine is given with cisapride, metoclopramide or domperidone, the gut motility properties of these drugs may be lessened due to the constipating effect of codeine.

Cimetidine may inhibit the metabolism of opiates.

The absorption of mexiletine may be delayed by codeine and as such the anti-arrhythmic effect may be lessened.

Naltrexone and naloxone antagonise the analgesic, CNS and respiratory depressant effect of opioids.

The hypotensive action of diuretics and antihypertensives may be potentiated by codeine.

Use of antidiarrhoeals and antiperistaltic drugs such as loperamide may induce severe constipation. Concurrent use of antimuscarinics may lead to a greater risk of severe constipation which subsequently causes paralytic ileus and/or urinary retention.

### 4.6 Pregnancy and lactation

Not recommended in pregnancy and lactation.

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 pharmacist or doctor regarding the use of Propain. Caution is advised in pregnancy and lactation with drugs containing morphine salts. No
teratogenicity is seen with antihistamines.

Codeine is 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.

Available published data do not contraindicate breast-feeding.

4.7 Effect on Ability to Drive and Use Machines

May cause drowsiness. If affected, do not drive or operate machinery. Avoid alcoholic drinks.

4.8 Undesirable effects

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

Codeine may cause nausea, vomiting, constipation and drowsiness in sensitive patients. Other side effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, respiratory depression, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, hallucinations, dysphoria, mood changes, miosis, decreased libido and potency, rashes, urticaria and pruritus. Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.

Drowsiness is seen with all of the older antihistamines such as diphenhydramine especially in high dosage. Also seen are headache, psychomotor impairment, antimuscarinic effects (e.g. urinary retention), dry mouth, blurred vision and gastro-intestinal disturbance. Other less common side effects that have been reported with antihistamines are: palpitations, arrhythmias, hypotension, hypersensitivity reactions (inc. bronchospasm, angioedema and anaphylaxis), rashes and photosensitivity, extrapyramidal effects, confusion, depression, sleep disturbance, tremor, convulsion, sweating, myalgia, paraesthesia, blood disorder, liver dysfunction and hair loss.

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: www.mhra.gov.uk/yellowcard.

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 carbamazepine, 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 deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdosage 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.

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 350 mg or a child more than 5 mg/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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol has analgesic (mainly peripheral) and antipyretic properties.
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.

Diphenhydramine hydrochloride is an antihistamine with sedative, antiemetic, anti-cholinergic and local anaesthetic properties. These actions are considered useful in those conditions for which Propain is indicated. Caffeine is a CNS stimulant and as such is used in combination with possible sedating analgesics.

5.2 Pharmacokinetic Properties

Paracetamol is readily absorbed from the gut to give peak blood levels in 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.

The elimination half-life ranges from 1 to 4 hours. Plasma binding is negligible. In overdose cases, accumulation of a hydroxylated metabolite may occur which may induce liver damage. Codeine Phosphate is readily absorbed from the gut. Peak blood levels occur approximately one hour after ingestion. Codeine is metabolised in the liver by O- and N-demethylation. The metabolites are excreted in the urine as glucuronic acid conjugates. The plasma half-life is approximately 3 to 4 hours. Diphenhydramine
Hydrochloride is readily absorbed from the gut. Peak blood levels occur approximately 2 to 4 hours after ingestion. It is metabolised and excreted in the urine. The metabolites are less readily cleared than the unchanged diphenhydramine. The plasma half-life is approximately 5 hours for diphenhydramine and 8 hours for total amines. The dose present in Propain is small when compared to the studies done to obtain these figures. Caffeine is readily absorbed from the gut. Peak blood levels occur approximately 1.5 hours after ingestion. The plasma half-life is approximately 3.5 hours. Codeine is almost completely metabolised and then excreted in the urine, mainly as L-methyluric acid and L-methylxanthine.

5.3. Preclinical Safety Data

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

Pharmaceutical Particulars

6.1. List of Excipients

Magnesium Stearate
Maize Starch
Talc
Methyl, ethyl, propyl and butyl parabens
Spirit of Chloroform
Gelatin
Quinoline yellow (E104)
Erythrosine (E127)
Purified Water

6.2. Incompatibilities

Not applicable in terms of solid medication.

6.3. Shelf Life

36 Months.

6.4. Special Precautions for Storage
6.5 Nature and contents of container
Blister: Lidding material - 35gsm Glassine paper/ad/9 micron soft temper Aluminium/compatible heat seal. Base material - 250 micron uPVC.
Pack sizes: 12, 16, 24, 32

6.6. Instructions for Use/Handling
None.

7 MARKETING AUTHORISATION HOLDER
Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)
PL 04416/0373

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
7 March 2000

10 DATE OF REVISION OF THE TEXT
01/03/2017