SUMMARY OF PRODUCT CHARACTERISTICS
Gigapyn ® Caplets

1. Name of the medicinal product

GIGAPYN Caplets

2. Qualitative and quantitative composition

Active ingredient	mg/tablet
Paracetamol Ph Eur	500.0
Codeine phosphate Ph Eur	8.00

3. Pharmaceutical form

Tablet

White capsule shaped tablet with a break line on both sides and embossed “P” and “C” on the separative halves.

4. Clinical particulars

4.1 Therapeutic indications

This medicine is indicated in patients older than 12 years of age.

For the short-term treatment of acute moderate pain which is not considered to be relieved by other analgesics (e.g. paracetamol, ibuprofen or aspirin) alone, such as: headache, period pains, neuralgia, toothache and rheumatic pains.

For oral administration.

4.2 Posology and method of administration

Adults: One to two caplets, taken with water every four to six hours if required, up to a maximum of 8 caplets in 24 hours.

Children aged 16 to 18 years:

One or two caplets every 6 hours when necessary up to a maximum of 8 caplets in 24 hours.

Children aged 12 to 15 years:

One caplet every 6 hours when necessary up to a maximum of 4 caplets in 24 hours.

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).

Elderly: The normal dose is considered appropriate in elderly patients.

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

4.3 Contraindications
Hypersensitivity to any of the ingredients. Severe liver disease.

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 with caution by patients with impaired kidney or liver function. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not take more medicine than the label tells you to.

If you do not get better, talk to your doctor.

Keep all medicines out of the reach of children.

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

The label will state:

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

Front of pack

• Can cause addiction

• For three days use only

Back of pack

• List of indications as agreed in 4.1 of the SPC

• 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 it 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 (or combined label/leaflet) will state:

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.

'Headlines' section (to be prominently displayed)

• This medicine can only be used for.....(indications)

• 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

'What this medicine is for' section

• Succinct description of the indications from 4.1 of the SPC

'Before you take this medicine' section

• 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

'How to take this medicine' section

• 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

• 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

'Possible side effects' section

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.go.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

'How do I know if I am addicted?' section

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 you doctor:

• You need to take the medicine for longer periods of time

• You need to take more than the recommended amount

• 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 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.

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 anticoagulation 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.

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter. The depressant effects of codeine are enhanced by depressants of the central nervous system such as hypnotics, sedatives tricyclic antidepressants and phenothiazines. Codeine may antagonise the gastrointestinal effects of metoclopramide and domperidone.

4.6 Fertility, pregnancy and lactation

The safety of paracetamol and codeine tablets during pregnancy has not been established and in view of the possible association of codeine with respiratory depression and heart malformations, use during this period should be avoided.

Codeine should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites 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. Available published data do not contraindicate breast feeding.

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. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

4.7 Effects on ability to drive and use machines

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 prescribing 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 a 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and

- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

- It was not affecting your ability to drive safely

4.8 Undesirable effects

The most common side effects are nausea, vomiting, constipation, dry mouth, sweating, skin rashes and other allergic reactions. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Paracetamol: very rare cases of serious skin reactions have been reported.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headaches can make them worse.

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 professional are asked to report any suspected adverse reactions via the Yellow Card Scheme at: 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, phenobarbitone, 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 overdosage. 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) but results should not delay initiation of treatment beyond 8 hours after ingestion, as 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.

Codeine

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

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. Hypotention and tachycardia are possible but unlikely.

Management 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 4 hours after ingestion.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Paracetamol is a peripherally acting analgesic with antipyretic activity.

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 readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half life varies from about 1-4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent.

Codeine phosphate is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by O- and N-Demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half life has been reported to be between 3 and 4 hours.

5.3 Preclinical safety data
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. Pharmaceutical particulars

6.1 List of excipients
Pregelatinized maize starch, maize starch, povidone (PVP – K30), potassium sorbate, purified talc, stearic acid, purified water.

6.2 Incompatibilities
None known.

6.3 Shelf life
Two years.

6.4 Special precautions for storage
Do not store above 30°C. Keep in tightly closed containers away from light.
KEEP OUT OF THE REACH OF CHILDREN

6.5 Nature and contents of container
In containers of 30's, 50's, 100's and 1000's (HDPE jar and LDPE closure, PP securitainer container and LDPE closure)
Push through blister packs of 10 caplets in a carton of 30's or 1000's.

7. Applicant and Principal

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9. Registration number(s)

TBA

10. Category of Distribution

Pharmacy Only

10. Pharmacological Classification

N02AJ Opioids in combination with non-opioid analgesics

11. Date of publication

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