SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rokacet
Rokacet Plus

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rokacet:
Each caplet contains paracetamol 500 mg, caffeine (anhydrous) 30 mg, codeine phosphate 10 mg.

Rokacet Plus:
Each caplet contains paracetamol 500 mg, caffeine (anhydrous) 50 mg, codeine phosphate 15 mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Caplets

Rokacet:
Yellow, oblong, bioconvexed, film-coated caplet. One side embossed with 'TARO'.

Rokacet Plus:
Light orange, oblong, bioconvexed, film-coated caplet. One side embossed with 'TARO'.

4 CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE
WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see section 4.5]
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
Limit dosages and durations to the minimum required.
Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

For the relief of pain and coughs and for the reduction of fever accompanied by pain.

4.2 Posology and method of administration

Adults (including the elderly)
2 caplets up to 3 or 4 times a day if necessary. The dose should not be repeated more frequently than every four hours, and not more than 4 doses (8 caplets) should be given in any 24 hour period.
Paediatric population:

Children aged 16-18 years:
1-2 caplets every 6 hours when necessary up to a maximum of 8 caplets in 24 hours.

Children aged 12 – 15 years:
1 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).

For oral administration 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

4.3 Contraindications

Hypersensitivity to paracetamol, caffeine, codeine, opioid analgesics or any of the other constituents listed in section 6.1.

In all paediatric patients (12-18 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 children under 12 years.

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

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.

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.

<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 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 European	1%-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.

Codeine Dependence

Rokacet and Rokacet Plus contain codeine whose regular or prolonged use may produce psychological and physical dependence. This product should be used with caution in patients with current or past history of substance abuse or dependence (including drug or alcohol) or mental illness (e.g., major depression). Abuse or misuse may result in overdose and/or death (see Section 4.9).

This medicine contains less than 1 mmol sodium (23 mg) per caplet, that is to say essentially 'sodium-free'.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total 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.

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.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Opiate analgesics may interact with monoamine oxidase inhibitors (MAOI) 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-caffeine-codeine during pregnancy has not been established relative to the possible adverse effects of foetal development and should be avoided during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

Lactation
Codeine should not be used 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.

Although significant caffeine toxicity has not been observed in breastfed infants, caffeine may have a stimulating effect on the infant.

Due to the caffeine content of this product it should not be used if you are pregnant or breastfeeding.

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.**

Caffeine

Body System	Undesirable effect
Central nervous system	Nervousness Dizziness

When the recommended paracetamol-caffeine-codeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

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.
Renal and urinary disorders	Difficulty with micturition
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

Overuse of this product, defined as consumption of quantites 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

An overdose of codeine is characterised, 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.

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.

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.

Caffeine

Symptoms and signs

Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Management

Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose, but can be considered for up to four hours after the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

Summary

Treatment of overdose with Rokacet and Rokacet Plus requires assessment of plasma paracetamol levels for antidote treatment, with signs and symptoms of codeine and caffeine toxicity being managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is a well established analgesic. Caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action.
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 almost completely absorbed from the gastrointestinal tract. Concentration of paracetamol in plasma reaches a peak in 30-60 minutes and the plasma half-life is 1-4 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 administration and distributes widely throughout the body. 85% of an oral dose is excreted in the urine within 24 hours, 40-70% of this being free or conjugated codeine, 5-15% free or conjugated morphine, 10-20% free or conjugated norcodeine, and trace amounts may be free or conjugated normorphine.

Caffeine is rapidly but irregularly absorbed after oral administration, absorption is pH-related. After an oral dose of 100 mg, peak plasma concentrations of 1.5-2μg/ml are attained within 1-2 hours. Plasma half-life = 4-10 hours. Caffeine rapidly distributes throughout the body water, and is approximately 15% bound to plasma proteins. In 48 hours, 45% of a dose is excreted in the urine as l-methylxanthine and 1-methyluric acid.

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

Rokacet:
Stearic acid, Opadry OY-L-28990 (lactose, hypromellose, polyethylene glycol), sodium starch glycolate, Opadry Yellow-31F32864 (lactose, hypromellose, titanium dioxide, polyethylene glycol, D&C yellow #10 lake, iron oxide yellow and iron oxide red).

Rokacet Plus:
Opadry OY-L-28990 (lactose, hypromellose, titanium dioxide, polyethylene glycol), stearic acid, sodium starch glycolate, Spectracol FD&C yellow #6 lake.

6.2 Incompatibilities

None stated.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/ PVDC aluminium foil blister in cardboard cartons.
Rokacet pack containing 4 or 20 caplets.
Rokacet Plus pack containing 2, 10, 12 or 24 caplets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MANUFACTURER AND REGISTRATION HOLDER

Taro Pharmaceutical Industries Ltd.
14 Hakitor St., Haifa Bay 2624761, Israel

8 REGISTRATION NUMBER(S)

Rokacet 027-84-21960-00
Rokacet Plus 040-48-25715-00

Revised in July 2022 according to MOH guidelines.