# 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, biconvexed, film-coated caplet. One side embossed with 'TARO'.

Rokacet Plus:
Light orange, oblong, biconvexed, 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

**Posology**

Adults

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:

Adolescents aged 16-18 years:

1-2 caplets every 6 hours when necessary up to a maximum of 8 caplets in 24 hours.

Adolescents 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 who are pregnant or breastfeeding (see section 4.6).

In children under 12 years.

In respiratory depression, chronic constipation.

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.

Paracetamol should be administered only with particular caution under the followingcircumstances:

- Hepatocellular insufficiency
- Chronic alcoholism
- Renal failure (GFR ≤ 50 ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphatase dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- The elderly, adults and adolescents weighing less than 50 kg

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5- oxoproline, is recommended.

Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy, hypothyroidism and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

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.

Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid since mild bronchospasms are reported in association with paracetamol (cross reaction).

Do not exceed the stated dose.
Patients should be advised not to take other paracetamol or codeine-containing products concurrently. Immediate medical advice should be sought in the event of

overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).

If symptoms persist for more than 3 days or get worse, or if any other symptoms occur, treatment should be discontinued, and a physician consulted.

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 (see section 4.9).

Patients taking, or who have taken, monoamine oxidase inhibitors (MAOIs) within the preceding two weeks (see section 4.5) should not take this product.

Codeine, as with other opioids should be used with caution in patients with hypotension, hypothyroidism, head injury or raised intracranial pressure.
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 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.

Codeine dependance, tolerance and potential for abuse:

Rokacet and Rokacet Plus contain codeine whose regular or prolonged use may produce psychological and physical dependence (addiction) even at therapeutic doses. This product should be used with caution in patients with current or past history of substance abuse or dependence (including drug or alcohol misuse) or mental illness (e.g., major depression) because the risks of drug dependence are increased. Abuse or misuse may result in overdose and/or death (see Section 4.9). Additional support and monitoring may be necessary when recommending Rokacet and Rokacet Plus for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

In case of misuse and if the product is used for longer than recommended, patients may find that treatment is less effective and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should beexplained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient misuses Rokacet and Rokacet Plus

and uses long-term opioid therapy and presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Drug withdrawal syndrome
Addiction can cause drug withdrawal syndrome upon abrupt cessation of therapy or dose reduction.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

*Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:*

Concomitant use of Rokacet and Rokacet Plus and sedative medicines such as benzodiazepines or related drugs (such as pregabalin and gabapentin) may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Rokacet and Rokacet Plus concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patientsand their caregivers to be aware of these symptoms (see section 4.5).

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 cholestyramine. Cholestyramine should not be administered within one hour of taking paracetamol.

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.

Paracetamol is metabolised in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or induce this route (e.g. barbiturates, such as phenobarbitone, tricyclic antidepressants, alcohol, carbamazepine, phenytoin, primidone, rifampicin, St John's wort or other drugs that induce liver enzymes),causing hepatotoxicity, particularly in overdose (see section 4.9).

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced because probenecid reduces the clearance of paracetamol by 50% since it prevents the conjugation of paracetamol with glucuronic acid.

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics, but its validity has been criticised and evidence of a clinically relevant interaction appears to be lacking. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

Caffeine

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers. Caffeine may enhance the tachycardia effect of some decongestants.

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.

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.

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. It is recommended that the product should not be taken concurrently or within two weeks of stopping treatment with a MAOI.

*Sedative medicines such as benzodiazepines or related drugs:*
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**
Rokacet and Rokacet Plus should not be used during pregnancy (see section 4.3). This includes maternal use during labour because of the potential for respiratory depression in the neonate.

Due to the caffeine-content of this product it should not be used during pregnancy.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

The patient should be advised of the risk of neonatal opioid withdrawal syndrome, and it should be ensured that appropriate treatment will be available.

Paracetamol
A large amount of data on pregnant women indicate neither malformative, nor foeto/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.

**Lactation**
Rokacet and Rokacet Plus should not be used during breastfeeding (see section 4.3), as codeine may be secreted in breast milk and may cause respiratory depression in the infant.
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 during breastfeeding.

**Fertility**
There are no data available regarding the influence of Rokacet and Rokacet Plus

onfertility.

## 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. 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 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, 363 <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

**Paracetamol**

| **Body System** | **Undesirable effect** | **Frequency** |
|---|---|---|
| Blood and lymphatic system disorders | Thrombocytopenia<br>Agranulocytosis | Not known |
| Immune system disorders | Anaphylaxis | Not known |
| | Allergies (not including angioedema) | Rare |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm* | Not known |
| Hepatobiliary disorders | Hepatic dysfunction | Not known |
| | Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema | Very rare |

| | | |
|---|---|---|
| Skin and subcutaneous tissue disorders | Very rare cases of serious skin reactions have been reported. Stevens Johnson syndrome(SJS), toxic epidermal necrolysis(TEN), drug-induced dermatitis, acute generalized exanthematous pustulosis (AGEP) | Very rare |
| Renal and urinary disorders | Sterile pyuria (cloudy urine) | Very rare |

*** 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** | **Frequency** | Frequency |
|---|---|---|---|
| Central nervous system | Nervousness<br>Dizziness | Not known | Not known |

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** | **Frequency** |
|---|---|---|
| Psychiatric disorders | Drug dependency can occur after prolonged use of codeine (see section 4.4) | Not known |
| Gastrointestinal disorder | Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis | Not known |
| Nervous system disorder | Dizziness,<br>Hyperalgesia<br>Drowsiness. | Not known |
| General disorders and administration | Drug withdrawal syndrome | Uncommon |
| Renal and urinary disorders | Difficulty with micturition | Not known |
| Skin and subcutaneous tissue disorder | Pruritus, sweating | Not known |

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 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. Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

**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.

**<u>Caffeine</u>**

**Symptoms**

Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, nervousness, 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

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics: codeine and paracetamol.
ATC code: N02AJ09

Paracetamol is a well-established analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action. Caffeine stimulates all levels of the CNS, although its cortical effects are milder and shorter than those of amphetamines.
Analgesia adjunct: caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhancing pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.
Caffeine enhances and prolongs the analgesic activity of paracetamol up to 3 hours.

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

Absorption

*Paracetamol* is rapidly and almost completely absorbed from the gastrointestinal tract. After oral administration, concentration of paracetamol in plasma reaches a peak in 10-60 minutes depending on pharmaceutical form.

*Caffeine* is rapidly but irregularly absorbed after oral administration; absorption is pH related. Maximum plasma concentrations are achieved within one hour and the plasma half-life is about 4.9 hours, but there are large inter-individual and intra-individual differences ranging between 1.9-12.2 hours.

*Codeine phosphate* is well absorbed from the gastrointestinal tract after oral administration with peak plasma concentration being reached in approximately 1 hour after ingestion.

Distribution

*Paracetamol* is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding.

*Caffeine* administered orally is practically fully bioavailable and distributes into all body fluids. The mean plasma protein binding of caffeine is 35%. Maximum plasma concentrations are reached after 30-40 minutes.

*Codeine* distributes widely throughout the body and exhibits low plasma protein binding with a plasma half-life of approximately 2.5 to 3 hours.

Biotransformation

*Paracetamol* is mainly metabolised in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinone imine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

*Caffeine* is almost completely metabolised in the liver by oxidation, demethylation and acetylation, and is excreted in the urine. The major metabolites are 1-methylxantine, 7-methylxantine, 1,7-dimethylxantine (paraxantine). Minor metabolites include 1-methyluric acid and 5-acetylamino-6-formylamino 3-methyluracil (AMFU).

*Codeine* is metabolised in the liver by the hepatic enzyme Cytochrome P450 2D6 (CYP2D6) to form morphine, and Cytochrome (CYP3A4) to form norcodeine, which are further metabolised by conjugation with glucuronic acid.

Elimination

Less than 5% is excreted as unmodified *paracetamol*; the elimination half-life varies from 1 to 4 hours. Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulfate conjugates (20-30%). In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. and the plasma half-life is 1-4 hours. Excretion is almost exclusively renal, in the form of conjugated metabolites.

*Caffeine* and its metabolites are primarily eliminated by the kidneys. Plasma half-life
= 4-10 hours. In 48 hours, 45% of a dose is excreted in the urine as l-methylxanthine and l-methyluric acid.

85% of an oral dose of *codeine* 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.

### 5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation oftoxicity to reproduction and development are not available.

## 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.
HDPE bottles and PP safety cap.
Rokacet pack contains 20 caplets.
Rokacet Plus pack contains 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 NUMBERS

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

Revised in November 2023 according to MOH guidelines.