Summary Product Characteristics

1. Name of the medicinal product
Costapyn Tablets

2. Qualitative and quantitative composition
Paracetamol 450.00mg
Codeine Phosphate 10.00mg
Doxylamine Succinate 5.00mg
Caffeine 30.00mg

For the Full list of excipients, See Section 6.1.

3. Pharmaceutical form
Uncoated Tablet (Tablet)

4. Clinical particulars
4.1 Therapeutic indications
For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone such as headache, tension headache, migraine, neuralgia, toothache, dysmenorrhoea, muscular and rheumatic achesand pains and post-operative analgesia following surgical or dental procedures.
Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is notconsidered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).*

4.2 Posology and method of administration
Posology
The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers shouldbe advised to seek the views of a physician. Do not take continuously for more than 3 days without consulting your doctor.
Adults
One or two tablets every four to six hours as needed for relief. Total dosage over a 24 hour period should not normallyexceed eight tablets.
Elderly and debilitated
Codeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to therespiratory depressant effects.
Paediatric population
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 thevariable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).
Children aged 16 years to 18 years
One to two tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.
Children aged 12 years to 15 years
One tablet every six hours when necessary to a maximum of 4 tablets in 24 hours
Method of administration
Oral use.

4.3 Contraindications
Hypersensitivity to paracetamol, codeine or other opioid analgesics, doxylamine succinate, caffeine, or any of the other constituents.
Due to interaction with the doxylamine succinate component, the concomitant use of Costapyn with monoamine inhibitors(MAOIs) or within 14 days of stopping treatment with these medicines is contraindicated, as there is a risk of serotonin syndrome (see section

4.5).
Conditions where morphine and opioids are contraindicated e.g:
• Acute asthma (during an attack)
• Acute respiratory depression and in chronic obstructive pulmonary disease
• Acute alcoholism
• Head injuries
• Raised intra-cranial pressure
• Following biliary tract surgery
• Risk of paralytic ileus
• Breast-feeding (see Section 4.6)
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 section4.4).
In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers.

4.4 Special warnings and precautions for use
Paediatric population
Not recommended for children under 12 years of age.
CY2D6 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 patientsconvert 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 (seealso 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 traumaor extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.
Do not exceed the stated dose.
Do not take concurrently with any other paracetamol or codeine containing compounds.This product may cause drowsiness.
Keep out of the reach and sight of children.
Care is advised in the administration of this preparation to patients with impaired kidney

or liver function and in those with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urinary retention, susceptibility toangle-closure glaucoma, shock, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of cardiac arrhythmias or convulsions, and in patients with a history of drug abuse or emotional instability.
Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and rarely colonicobstruction. Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.
Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI)has been associated with very severe and sometimes fatal reactions. See also Section 4.3 regarding contraindication of taking Costapyn with MAOIs because of the doxylamine component.
Risks from concomitant use of opioids and benzodiazepines
Concomitant use of opioids, including codeine, and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of sedativemedicines, such as benzodiazepines or related drugs, with opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe codeine concomitantly with sedative medicines such as benzodiazepines, the lowesteffective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation . In this respect, it is strongly recommended to inform patients and their environment to beaware of these symptoms (see section 4.5).
Risks from concomitant use of opioids and alcohol
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma anddeath. Concomitant use with alcohol is not recommended (see section 4.5).
The hazards of overdose are greater in those with non-cirrhotic alcoholic liver diseases. Co-administration of enzyme-inducing antiepileptic medications may increase toxicity; doses should be reduced.E110 (sunset yellow) and E104 (quinoline yellow) may cause allergic reactions.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactosemalabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.The label will state:
Front of Pack:
• Can cause addiction
• For three days use only
Back of Pack:
• For the short term treatment of acute moderate pain where other painkillers have not worked. Do not take less than fourhours after taking other pain killers. This medicine is used for tension headaches, migraines, muscular pains and tension.
• Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
• Do not take anything else containing paracetamol whilst taking this medicine.
• Talk to your doctor at once if you take too much of this medicine, even if you feel well.
• 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 youtake this medicine for headaches for more than three days it can make them worse.
4.5 Incompatibilities: Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeine- phenobarbitone complex, and with potassium-iodide, forming crystals of codeine periodide. Acetylation of codeinephosphate by aspirin has occurred in

solid dosage forms containing the two drugs, even at low moisture levels.
Interference with laboratory tests: Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter ofOddi and increase biliary tract pressure.
The metabolism of paracetamol is possibly accelerated by carbamazepine, phenytoin, phenobarbital, primidone (alsothere have been isolated reports of hepatotoxicity)"

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommendeddosage, but patients should follow the advice of their doctor regarding its use.
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.
Codeine crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible associationwith respiratory and cardiac malformations has been reported. Regular use during pregnancy may cause physical dependence in the foetus leading to withdrawal symptoms in the neonate. Use during pregnancy should be avoided if possible. Use of opioid analgesia during labour may cause respiratory depression in the neonate, especially the prematureneonate. These agents should not be given during the delivery of a premature baby.

Breastfeeding

Paracetamol is excreted in breast milk but not in a clinically significant amount.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, higherlevels of the active metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

4.7 Effects on ability to drive and use machines

Some side effects related to doxylamine succinate include drowsiness (usually diminishes within a few days), paradoxical stimulation, headaches, psychomotor impairment, hypotension, dizziness, confusion, tremor and convulsions.
Opioid analgesics can impair mental function and cause blurred vision and dizziness. Rare side effects may includeconvulsions, hallucinations, blurred or double vision, dizziness and orthostatic hypotension
These side effects may have a noticeable impact on the ability to driving and operate machinery. Patients should ensurethey are not affected before driving or operating machinery.
See section 4.8 for more information on side effects.
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, patientsshould 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 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 medicineand
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse effects of doxylamine succinate:

Common side effects:

CNS effects: Drowsiness (usually diminishes within a few days), paradoxical stimulation, headaches, psychomotorimpairment.

Antimuscarinic effects: Urinary retention, dry mouth, blurred vision, gastrointestinal disturbances, thickened respiratorytract secretions

Rare side effects:

Hypotension, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions,palpitation, arrhythmia hypersensitivity reactions, blood disorders and liver dysfunction.

Adverse effects of paracetamol:

Blood and lymphatic system disordersVery rare: thrombocytopenia Not known: agranulocytosisImmune system disorders

Hypersensitivity including skin rash may occur.Not known: Anaphylactic shock, angioedema. Skin and subcutaneous tissue disorders

Very rare cases of serious skin reactions have been reported.

Adverse effects of Codeine:

The most frequent undesirable effects of codeine are constipation and drowsiness. Less frequent effects are nausea,vomiting, sweating, facial flushing, dry mouth, blurred or double vision, dizziness, orthostatic hypotension, malaise, tiredness, headache, anorexia, vertigo, bradycardia, palpitations, respiratory depression, dyspnoea, allergic reactions (itch, skin rash, facial oedema) and difficulties in micturition (dysuria, increased frequency, decrease in amount). Sideeffects, which occur rarely, include convulsions, hallucinations, nightmares, uncontrolled muscle movements, muscle rigidity, mental depression and stomach cramps. Very rare cases of pancreatitis have been reported.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may resultwhen treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions

Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamolmay 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 orother 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. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin may occur and the INR may increase. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding and death.

Acute renal failure with acute tubular necrosis, strongly suggestedby 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 tonausea 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. Ifvomiting 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 signsuntil 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-lifeso 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 - analgesic, antipyreticCodeine Phosphate - analgesic Doxylamine Succinate - antihistamineCaffeine - mild stimulant

Pharmacotherapeutic group: Anilides, Paracetamol combinationsATC Code: NO2B E51

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits 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

The pharmacokinetics of paracetamol, codeine phosphate and caffeine are widely published (see Goodman and Gilman's Pharmacological Basis of Therapeutics, Seventh Edition pgs. 693, 505 and 596 respectively. Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration the effects start within 15 to

30minutes and peak within one hour. In humans 60 - 80% of doxylamine given has been recovered in urine at 24 hours post-dose.
The bioavailability of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately
Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O- demethylation leading to morphine, N-demethylation to nor codeine and both O- and N-demethylation to normorphine. Morphine and nor codeine are further transformed to glucuronide conjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h (84.4±15.9%).
The O-demethylation of codeine to morphine is catalyzed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine.
Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

5.3 Preclinical safety data
None stated
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
Croscarmellose Sodium Microcrystalline cellulose PH 101 Sodium starch glycolate Povidone Tartrazine yellow water soluble Magnesium
Stearate
Aerosil

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C in the original packaging to protect from moisture.

6.5 Nature and contents of container
PVDC coated PVC 90 gsm

6.6 Special precautions for disposal and other handling
Not applicable

7. Marketing authorisation holder
Cosmos Limited Rangwe close Off lunga lunga road
Nairobi Kenya 41433-00100

8. Market Authorization Number
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9. Date of First Authorization
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10. Date of Revision of Text
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