Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Co-Tipol 500 mg/30 mg suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 500mg paracetamol and 30mg codeine phosphate hemihydrate.
Excipient with known effect: contains 12.5 mg of soya lecithin per suppository.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository

White to ivory coloured, torpedo shaped suppository

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults: Moderate to severe pain.
Children 12-18 years: Co-Tipol is only suitable for use in children older than 12 years for treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol and ibuprofen (alone).

4.2 Posology and method of administration

Posology

Age	**Bodyweight**	**Single dose**	**Maximum daily dose(24hours)**
Adults and children above 12 years of age	More than 43 kg	1 – 2 suppositories (equivalent to 500 – 1000 mg paracetamol and 30—60 mg codeine phosphate hemihydrate)	5 - 8 suppositories (equivalent to 2500 – 4000 mg paracetamol and 150 - 240 mg codeine phosphate hemihydrate)

The maximum daily dose (8 suppositories in 24 hours) must not be exceeded, and the interval between doses should be at least six hours (if any further suppositories are needed).

This product should not be used with other paracetamol or codeine-containing medicines.

Co-Tipol should be used at the lowest effective dose for the shortest period of time. This dose may be used, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240mg.

Renal and hepatic impairment
The dose should be reduced or the interval between doses should be increased in the presence of impaired liver and/or kidney function and in subjects suffering from Gilbert's syndrome (Meulengracht's disease). Patients with severe renal impairment (creatinine clearance < 10 ml/min) must not exceed a dose interval of at least 8 hours.

The elderly:
A reduced dose may be required (see section 4.4). Experience has indicated that normal adult dosage of paracetamol is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

Paediatric population
Children and adolescents with a low body weight.

The administration of Co-Tipol 500 mg / 30 mg is not recommended for children below 43 kg bodyweight as the dosage strength is not suitable for this patient group.

Co-Tipol 500 mg / 30 mg 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).

Method of administration

Suppositories are for rectal use.

The suppositories are introduced deeply into the anus after defecation. In order to improve the lubricating sliding property, the suppositories may be warmed in the hands or briefly immersed into hot water.

Duration of treatment

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

Co-Tipol is contraindicated in:
- patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- patients with known hypersensitivity to soya or peanut
- patients with respiratory insufficiency
- patients with pneumonia
- patients with acute asthma
- oncoming childbirth
- imminent premature birth
- children under 12 years of age or less than 43kg body weight
- women who are breastfeeding (see section 4.6).

- patients who are known to be ultra-rapid metabolisers for CYP2D

- 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).

- children with compromised respiratory function

4.4 Special warnings and precautions for use

In order to avoid overdosing, it should be ensured that no other medications containing paracetamol and/or codeine are administered concurrently.

Co-Tipol should only be administered upon careful evaluation of the risk-benefit ratio in the following cases:

- opioid dependence
- disorders of impaired consciousness
- increased intracerebral pressure
- concurrent use of MAO-inhibitors
- chronic obstructive pulmonary disease

CONTAINS PARACETAMOL.

Do not use with other paracetamol or codeine containing medicines.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

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 ultrarapid 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Co-Tipol and sedative medicines such as benzodiazepines or related drugs 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 Co-Tipol 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 patients and their caregivers to be aware of these symptoms (see section 4.5).

Severe acute hypersensitivity reactions such as anaphylactic shock have very rarely been seen. Treatment should be discontinued at the earliest signs of hypersensitivity reactions to the use/administration of Co-Tipol. Hypersensitivity reactions require urgent treatment by experienced clinicians.

Severe liver damage may result from exceeding the recommended dose.

If large amounts of paracetamol are taken for extended periods of time or if this medicinal product is not used properly, it may cause headache which should not be treated with increased doses. In such cases, treatment should not be continued without first seeking the advice of a medical practitioner.

In general, the long-term use of analgesics, above all in combination with pain killers having an anti-inflammatory and antipyretic action, may lead to permanent damage to the kidney, which might result in renal failure (analgesic nephropathy).

Headache, fatigue, muscular pain, nervousness and vegetative symptoms may occur after abrupt discontinuation of any analgesic not used as directed or taken in large doses over long periods of time. No analgesic should be taken before subsidence of such symptoms, which usually disappear within a few days. A physician should be consulted before resuming treatment.

Co-Tipol should not be used in high dosage by patients suffering from hypotension and hypovolaemia.

This fixed-combination drug contains codeine. As a component of a fixed dose mixture, codeine exhibits a primary potential for dependence. The prolonged use of large amounts of such products results in the development of tolerance, psychological and physical dependence. Cross-tolerance to other opioids is induced. Patients with pre-existing opiate dependence – even those in remission – are likely to suffer a quick relapse.
Codeine is regarded as a substitute by heroin addicts. Persons addicted to alcohol and sedatives are also prone to codeine abuse.

Medicinal products containing codeine are available on prescription only and should be used under close medical supervision. It is irresponsible to pass medicines prescribed for use by the patient on to other persons.

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.

Caution:
The prolonged administration of large amounts increases the risk of producing dependence.
Patients receiving large doses and very sensitive persons may develop dose-related disturbances of visuomotor coordination and impaired visual acuity. Furthermore, respiratory depression and euphoria may occur.

Caution must be exercised in the treatment of patients having undergone cholecystectomy. Myocardial infarction-like symptoms may occur and symptoms of patients with pancreatitis may become worse as a result of a contraction of the Sphincter of Oddi.

4.5 Interaction with other medicinal products and other forms of interaction

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).

The concomitant use of drugs which lead to an enzyme induction in the liver, such as specific sedatives and antiepileptic drugs (among others phenobarbital, phenytoin, carbamazepine) as well as rifampicin may lead to liver damage even in otherwise innocuous dosages of paracetamol

The same applies to compounds that may have a toxic action on the liver and to alcohol abuse.

The concomitant use of drugs that lead to slow gastric emptying may decelerate the onset the action and speed of absorption of paracetamol.

Conversely, the absorption of paracetamol may be enhanced and the drug may have a more rapid onset of action, if the patient concurrently receives drugs accelerating gastric emptying like metoclopramide or domperidone.

Patients who concomitantly receive paracetamol and zidovudine (AZT or retrovir) may be more susceptible to the development of neutropenia.

Ingestion of probenecid inhibits the linkage of paracetamol to glucuronic acid, reducing paracetamol clearance by a factor of about 2. The dose of paracetamol should therefore be reduced if probenecid is given concurrently.

Cholestyramine reduces the absorption of paracetamol.

Alcohol should be refrained from by patients on Co-Tipol, since their psychomotor performance may be substantially impaired (overadditive effect of the different ingredients).
When administered in combination with chloramphenicol, Co-Tipol may substantially slow down the excretion and increase the toxic risk of this compound.

Salicylamides may increase the elimination half-life of paracetamol.

Anticoagulants: The repeated ingestion of paracetamol for more than one week reinforces the response to anticoagulants, while the occasional use of paracetamol has no significant influence on the effect of these drugs.

Codeine-induced respiratory depression may be increased in subjects receiving tricyclic antidepressants (imipramine, amitriptyline) or opipramol.

The concomitant use of MAO inhibitors like tranylcypromine may reinforce the action on the central nervous system and produce other side-effects of unforeseeable severity. That is why Co-Tipol should not be used within two weeks after the last administration of any MAO inhibitor.

This medicinal product increases the effect of analgesics. Its action may be diminished by the simultaneous use of partial opioid agonists and antagonists such as buprenorphine and pentacozine.

Cimetidine and other drugs influencing the liver metabolism may increase the effect of Co-Tipol. Inhibition of morphine degradation resulting in an elevation of plasma levels was seen in patients on morphine treatment. This effect cannot be ruled out for codeine.

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).

Effect on laboratory findings:

Uric acid tests using phosphotungstic acid and the determination of blood glucose with glucose oxidase peroxidase may be influenced by paracetamol.

4.6 Fertility, pregnancy and lactation

Pregnancy

An association was noted between malformations of the respiratory tract and the use of codeine in the first three months of human pregnancy. Epidemiological studies of narcotic analgesics including codeine have revealed further malformations.

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, Co-Tipol should only be used during pregnancy – especially in the first three months – if clinical circumstances so indicate and after balancing benefits against risks.

The use of Co-Tipol is contraindicated in women well advanced in pregnancy or at risk for premature delivery, since codeine can cross the placental barrier and cause respiratory depression in the newborn.

The prolonged use of codeine may give rise to opioid dependence of the foetus.
The repeated administration of codeine in the last three months of pregnancy has been reported to cause withdrawal symptoms in the newborn.

Breast-feeding

Co-Tipol 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 ultrarapid 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.

4.7 Effects on ability to drive and use machines

Even if used properly, the codeine component of Co-Tipol may modify the patient's reaction to an extent that his/her ability to drive a car, operate machinery or perform hazardous activities is impaired.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Allergic thrombocytopenia, leucocytopenia	Agranulocytosis, pancytopenia
Nervous system disorders	Dizziness, mild headache, fatigue	Mild drowsiness	Sleep disturbances		
Ear and labyrinth disorders			Tinnitus		
Respiratory, thoracic and mediastinal disorders			Shortness of breath		Bronchospasm (analgesic asthma syndrome)
Gastrointestinal disorders	Nausea, vomiting (initially), constipation		Dry mouth		
Hepatobiliary disorders				Increase in liver-specific laboratory findings	

				(increase of liver transaminase level)	
Skin and subcutaneous tissue disorders			Pruritus, erythema, allergic exanthema, urticaria		Serious skin reactions (including Stevens-Johnson syndrome)
Immune system disorders					hypersensitivity reactions such as angioedema, shortness of breath, sweating, nausea, fall in blood pressure, including shock

Note:
Patients should be instructed to stop treatment and immediately contact a doctor at the earliest signs of hypersensitivity reactions.
Allergic reactions caused by non-fat phospholipids from soybeans are very rare.

Description of selected adverse reactions
Pulmonary oedema: Patients on large doses may develop pulmonary oedema, especially those with pre-existing disorders of lung function.
Cardiovascular diseases: Patients taking large amounts tend to develop fall in blood pressure and syncope.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, Dublin D02 XP77, Ireland; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The symptoms of an overdose with Co-Tipol correspond to the manifestations of poisoning with the single agents.

Paracetamol

Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency Procedure:

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

Codeine

Respiratory depression is a characteristic symptom of codeine overdosage. Furthermore, somnolence including stupor and coma, as well as vomiting, headache, urinary and faecal retention and sometimes bradycardia and a fall in blood pressure may occur. Seizure disorders have been reported occasionally, especially in children.

These symptoms may be intensified by the simultaneous ingestion of alcohol or drugs producing a sedative effect on the CNS. The elderly, patients with liver or renal disease, patients with compromised respiratory function, children under 18 years and ultra-rapid metaboilisers for CYP2D6 are at a higher risk of toxic symptoms.

Codeine may increase the smooth muscle tone, especially after the ingestion of single doses over 60 mg.

In the event that amounts exceeding 2 mg of codeine per kg bodyweight have been ingested and if the patient develops clinical symptoms, respiration should be monitored and resuscitation should be available until subsidence of symptoms. In the absence of clinical symptoms, these measures should be taken for a period of up to six hours.

The effect of codeine may be blocked in manifest respiratory depression by administration of opiate antagonists such as Naloxone. The administration of Naloxone is to be repeated because the period of action of codeine lasts longer than that of Naloxone. If Naloxone cannot be administered, symptomatic measures, in particular, putting the patient in recovery position, ventilation and shock treatment are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics and antipyretics, anilides
ATC-Code: N02AJ06

Paracetamol is an analgesic and antipyretic agent having a very weak anti-inflammatory action. Its mode of action is still not entirely clear.

However, it is well established that paracetamol inhibits the central prostaglandin synthesis to a far greater extent than the peripheral one. Furthermore, it counteracts the effect of the endogenous pyrogens on the hypothalamic heat-regulating centre. It may be assumed that there is a correlation between this mechanism and its antipyretic 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.

In clinical studies, the association of paracetamol and codeine has been compared with various analgesics and with placebo. In all cases, the fixed dose mixture was shown to be significantly superior to placebo. The results of certain studies suggest that

the combination produces a stronger analgesic effect than the single compounds, even after an increase in their doses, providing the risks associated with drug mixtures are found to be acceptable.

5.2 Pharmacokinetic properties

Paracetamol

Absorption:

Paracetamol is rapidly and completely absorbed with oral administration. (0,5 – 1,5 hours until the maximum serum levels are reached).Concentration in plasma reaches a peak in 30-60 minutes upon administration.

It is widely metabolized in the liver by direct conjugation with glucoronic acid or sulfuric acid. A small part is metabolized through the Cytochrome P450 system (mainly CYP2E1) resulting in the production of the toxic metabolite N-acetyl-p-benzochinonimine that is normally bound and excreted, the concentration is increased, however, in the event of massive intoxication.

Elimination:

The drug is eliminated via the kidney. Ninety percent of the absorbed amount is eliminated via the kidneys mainly as glucuronides (60 to 80 %) and sulfate conjugates (20 to 30 %) within 24 hours. Less than 5 % remain unchanged and is thus eliminated. The elimination half life amounts to approx. two hours. In cases of renal disorder or after overdose or in newborns the half life is prolonged.

The maximum action and the average period of action (4 to 6 hours) correlate approx. with the plasma concentration.

Renal impairment:

In cases of severe renal insufficiency (creatinine clearance < 10 ml/min) the elimination of paracetamol and its metabolites is retarded.

Codeine

Absorption:

Codeine is rapidly absorbed after oral administration. Concentration in plasma reaches a peak within approx. one hour.

It is metabolized in the liver (huge interindivudual differences).

The main metabolites are morphine, norcodeine as well as morphine and codeine conjugates. The conjugate levels are substantially higher than that of the parent substances.

Elimination:

The elimination half life of 3 to 5 hours is prolonged to 9 to 18 hours in cases of renal insufficiency and is also prolonged in elderly patients. The substance is eliminated mainly via the kidneys and approx. 10 % of codeine remains unchanged and is thus eliminated.

Codeine passes through the placenta barrier and enters the fetal circulation. Pharmacologically relevant concentrations are reached in the breast milk after high doses of codeine are administered.

Paracetamol and codeine show similar absorption speed and time of plasma concentration peaks as well as approx. same period of action. Furthermore, their biotransformation steps do not obstruct each other and no obstruction is given in the elimination via the kidneys.

5.3 Preclinical safety data

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat
Soya lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Aluminium/PE blister strips containing 5 suppositories.

Pack sizes: 10, 25, 50 and hospital pack sizes of 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
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8 MARKETING AUTHORISATION NUMBER

PA0126/332/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th November 2013
Date of last authorisation: 28th November 2018

10 DATE OF REVISION OF THE TEXT

September 2022