Front

Back

240mm

150mm

PARALGIN® FORTE TABLET
PARALGIN® TABLET

GoodScience

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)
Each tablet contains:
Paralgin®
Paracetamol 500mg, Codeine phosphate hemihydrate 8mg.

Paralgin® Forte
Paracetamol 400mg, Codeine phosphate sesquihydrate 30mg.

Product Description
Paralgin® Tablet is white, round convex, 13mm diameter tablet, inscribed with "SL" logo on one side and the other plain.

Paralgin® Forte Tablet is white, round convex, 12mm diameter tablet inscribed with "SL" logo on one side and breakline on the other

Pharmacodynamics
Pharmacotherapeutic group: Anilides, Paracetamol combinations
ATC Code: N02BE51

Paracetamol appears to produce analgesia at a subcortical site of brain, and may also block pain impulses by a depressant effect on peripheral chemoreceptors, mainly by inhibiting and interfering with the prostaglandin synthesis. Paracetamol lowers body temperature by acting in the hypothalamus to produce antipyresis.

Codeine phosphate has a central action especially in the cortex, thereby raising the threshold for pain.

Pharmacokinetics
Absorption
After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma level occurs 30-120 minutes after administration. Food intake delays paracetamol absorption. Codeine has about one-sixth of morphine's analgesic activity. It is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption.

Distribution
Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg. Paracetamol can cross the placenta and is excreted in milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism
Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). A minor proportion (less than 20%) is metabolised to catechol derivatives, and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant. Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

Excretion
Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1-4 hours. Codeine is metabolised in the liver to morphine, which with codeine, are excreted in the urine, partly as conjugates with glucoronic acid. Excretion is almost complete within 24 hours.

Indication
Paralgin® / Paralgin® Forte is indicated for the relief of painful disorders such as headache, dysmenorrhea, conditions involving musculoskeletal pain, myalgias, and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections.

Paralgin® / Paralgin® Forte is an effective analgesic after dental work and tooth extractions.

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

Recomended Dose
Adults and children over 12 years:
Two tablets, to be taken with a glass of water, not more frequently than every 4 hours, do not exceed 8 tablets in any 24 hours period.

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 the variable and unpredictable metabolism of codeine to morphine.

Paralgin® Paralgin® Forte is contraindicated in children below the age of 12 years for the symptomatic treatment of cold.

Children aged 12 years to 18 years
Paralgin® / Paralgin® Forte is not recommended for use in children aged 12 years to 18 years with compromised respiratory function.

Route of administration
Oral

Contraindication
- Hypersensitivity to the active ingredients or any of the excipients used in this product.
- Acute hepatitis. It should be given with care to patients with impaired kidney or liver function, also patients taking other drugs that affect the liver.
- It must not be used in patients with known glucose-6-phosphate-degydrogenase deficiency, patients with severe hepatocellular insufficiency, or severe respiratory disease, acute respiratory disease and respiratory depression, for example acute asthma, acute exacerbations of chronic obstructive pulmonary disease since codeine may exacerbate the condition.
- In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions.
- In all paediatric patients (0-18 years of age) who undergo tonsillectomy or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life-threatening adverse reactions.
- In women who are breastfeeding.
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- Codeine in contraindicated in the event of impending childbirth or in case risk of premature birth.

Warnings and Precautions

This preparation contains PARACETAMOL.
Do not take any other paracetamol containing medicines at the same time.

Allergy alert: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blister or rash. These could be sign of serious condition. If these reactions occur, stop use and seek medical assistance right away.

Do not exceed the recommended dose. At high doses codeine has most of the disadvantages of morphine, including respiratory depression. Codeine can produce drug dependence and therefore has the potential of being abused. Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks.

Caution is advised when codeine is used in patients with underlying respiratory conditions, including those with asthma and other chronic breathing problems.

Parents and caregiver of paediatric patients should be advised on the possible sign and symptom of respiratory depression in their children such as unusual sleepiness, confusion and difficult or noisy breathing and to seek immediate medical attention if these are observed.

Risk from Concomitant Use with Benzodiazepines
Profound sedation, respiratory depression, coma and death may result from the concomitant use of Paralgin® / Paralgin® Forte with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risk of respiratory depression and sedation when Paralgin® / Paralgin® Forte is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepines have been determined. Screen patients for risk of substance use disorders, including opioids abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Interactions with Other Medicaments).

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 these enzymes an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of Causian population may have this deficiency. However, if the patients is an extensive of ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity event at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioids 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 metabolizers in different populations are summarized below:

Population	Prevalence%
African/Ethiopian	29%
African American	3.4 to 6.5%
Asian	1.2 to 2.0%
Caucasian	3.6 to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. 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 metabolizers in their ability to metabolize 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.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening conditions, have been reported during concurrent use of Paralgin® / Paralgin® Forte with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and / or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Paralgin® / Paralgin® Forte if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness and low blood pressure. If adrenal insufficiency is suspected confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/ Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Post-marketing Experience)

Interactions with Other Medicaments
Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Anticoagulant dosage may require reduction and patients should be monitored for appropriate coagulation and bleeding complications.

Paracetamol absorption is increased by drugs, which increase gastric emptying, e.g. metoclopramide or domperidone, and decreased by drugs, which decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations. The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), hypnotics, rifampicin and alcohol.

When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Paralgin® / Paralgin® Forte and Zidovudine should be avoided.

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

Concurrent administration of sedatives or tranquillises may enhance the potential respiratory depressant effects of codeine.

Patients receiving other narcotic analgesics, antitussives, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol, gabapentinoids, cannabis, centrally-active anti-emetics) concomitantly with this codeine-containing drug may exhibit additive CNS depression.

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The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended.

A codeine-induces respiratory depression can be potentiated by tricyclic antidepressants.

Concomitant administration of Monoamide Oxidase Inhibitors (MAOIs) can potentiate the central nervous effects and other side effects of unpredictable severity. Codeine should not be used within two weeks after the discontinuation of MAOI treatment.

Concomitant use of codeine with anti-peristaltic anti-diarrhoeal drugs can increase the risk of severe constipation and CMS depression.

Morphinic agonist-antagonist- Concomitant use of codeine with a partial agonist (e.g buprenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

CYP2D6 inhibitors: Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, adjustment of the treatment should be considered.

CYP3A4 inducers: Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at Gab A sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warning and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Paralgin® / Paralgin® Forte if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

Pregnancy and Lactation
Pregnancy
Careful consideration should be given before prescribing the product for pregnant patients. Opioids analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

As a precautionary measures, use of Paralgin® / Paralgin® Forte should be avoided during the third trimester of pregnancy and during labour.

Breastfeeding
Paralgin® / Paralgin® Forte is contraindicated in women during breastfeeding.

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 patients is an ultra-rapid metabolizer 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.

Nursing mothers should also be advised to exercise caution when taking codeine since codeine's metabolite (morphine) subsequently be found in the breast milk. If the infant shows sign of increased sleepiness, difficulty breastfeeding, breathing difficulties and limpness, immediate medical attention should be sought.

Side Effects
Paracetamol
Reports of adverse reactions are rare. Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refused: dyspepsia, sweating, erythema, urticaria, anaphylactic shock, angioneurotic oedema, difficulty breathing, drop in blood pressure nausea, allergic reactions such as skin rashes, and haematological reactions, including thrombocytopenia, leukopenia, neutropenia, agramulocytosis and pancytopenia. Bronchospasm may be triggered in patients having a tendency of analgesic asthma. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption and cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.

Haemolytic anaemia, particularly in patients with underlying glucose-6-phosphate-dehydrogenase deficiency has been reported. Kounis syndrome and bronchospasm have also been reported.

Codeine
Nausea and vomiting, constipation, dizziness and drowsiness have been reported at therapeutic doses. Very rarely, skin rashes may occur in patients hypersensitive to codeine. There have also been very rare reports of pancreatitis. Others adverse reactions reported to be associated with codeine include: confusional state, dysphoria, euphoria, seizure, headache, somnolence, fatigue, hypotension, sedation, respiratory depression, dry mouth, pruritus, miosis, tinnitus and urinary retention. Visuomotor coordination and visual acuity may be adverse affected in a dose-dependent manner at higher doses or in particularly sensitive patients. Long term use also entails the risk of drug dependence.

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis have been reported.

Postmarketing Experience:
Serotonin syndrome

Adrenal insufficiency

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Symptoms and Treatment of Overdose
Overdose
Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzyme-inducing drugs are at an increased risk of intoxication, including fatal outcome.

Symptoms
Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma. Nausea, vomiting, anorexia, pallor and abdominal pain generally appear during the first 24 hours of overdosage with paracetamol. Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage. It can also lead to pancreatitis, acute renal failure and pancytopenia. The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15g (30 tablets) of paracetamol; a dose of 25g (50 tablets) or more is potentially fatal. Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop.

The ingestion of very high doses of codeine can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

Treatment
Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.

Consists primarily of management of paracetamol toxicity; naloxone is the treatment of choice for codeine intoxication.

Determinations of the plasma concentration of paracetamol are recommended.

Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Where paracetamol intoxication is suspected, intravenous administration of SH group donators such as acetylcysteine within the first 10 hours after ingestion is indicated. Although acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case it is taken for longer.

In cases of overdosage, methods of reducing the absorption of ingested drug are important.

Prompt administration of 50g activated charcoal and 500ml iced mannitol 20% by mouth may reduce absorption.

If the history suggests that 15g paracetamol or more has been ingested, administer one of the following antidotes:

Acetylcysteine 20% i.v
Administer 20% acetylcysteine (Parvolex, David Bull) immediately without waiting for positive urine test or plasma level results: initial dose 150mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and 100mg/kg in 1L 5% glucose over 16 hours; or

Oral Methionine
2.5g immediately followed by three further doses of 2.5g at four hourly intervals. For a 3-year-old child, 1g methionine 4-hourly for four doses has been used.

If more than ten hours have elapsed since the overdosage was taken, the antidote may be ineffective.

Relating to codeine component:
In general, treatment should be symptomatic: re-establish adequate respiratory exchange by ensuring a clear airway and using mechanical ventilation. When treatment for paracetamol toxicity has been initiated the opioid antagonist naloxone hydrochloride is an antidote to respiratory depression; naloxone 400 microgram may be administered SC, IM or IV; IV may be repeated at intervals of 2 to 3 minutes if necessary. Assisted respiration may be required,

Further measures will depend on severity, nature and course of clinical symptoms of intoxication and should follow standard intensive care protocols.

Effects on Ability to Drive and Use Machine
Paralgin® Paralgin® Forte may cause drowsiness, disturbances of visuomotor coordination and visual acuity. Due to preparation's sedative action, impairment of the mental and/or physical abilities required for the performance of potentially hazardous activities may occur. Hence children engaging in bike riding and other hazardous activities should be supervised to avoid potential harm.

Patients should not drive, operate machinery, or drink alcohol whilst taking this medication.

Storage Condition
Store in a dry place at below 30˚C protect from direct light and humidity.

Shelf Life
Paralgin® Tablet: 3 years
Paralgin® Forte Tablet: 4 years

Pack Size
Paralgin® Forte:
1. Blister pack of 60x15's / box
2. Blister pack of 2x15's / box

Paralgin®:
1. Blister pack of 100 x 10's /box

Name and Address of Manufacturer and Product Registration Holder
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