Panadeine Tablet

Analgesic-antipyretic

Paracetamol 500mg
Codeine Phosphate 8mg

For relief of moderate pain and fever **[SANOFI LOGO]**

Description
Each tablet contains 500mg paracetamol and 8mg codeine phosphate.
It is a round, white, flat, bevelled edge tablet with characteristic marking.

Indications
Panadeine 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. Panadeine is an effective analgesic after dental work and tooth extractions.

Codeine is not recommended for the treatment of post-operative pain following surgical procedures such as tonsillectomy or adenoidectomy in children and adolescents below 18years old due to the increased risk of respiratory depression.

Dosage and Administration
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 hour period.

Children and adolescents
Children aged less than 12 years: Codeine is contraindicated 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.
In those 12 years old and above, codeine may be used for the short-term treatment of acute moderate pain which is not relieved by analgesics such as ibuprofen or paracetamol alone. The lowest effective dose should be used for the shortest possible duration.

Children aged 12 years to 18 years: Panadeine is contraindicated for use in children aged 12 years to 18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea.

Contraindications
Panadeine must not be used in patients with known hypersensitivity to paracetamol, codeine or any of the excipients used in this product. It must not be used in patients with known glucose-6-phosphate-dehydrogenase 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.

Panadeine is contraindicated for use in patients who are:
- younger than 12 years (see section Special Warnings and Precautions for use)
- aged between 12-18 years in whom respiratory function might be compromised including post tonsillectomy and/or adenoidectomy to treat obstructive sleep apnoea, due to an increased risk of developing serious and life-threatening adverse reactions (see section Special Warnings and Precautions for use)
- breastfeeding (see section Pregnancy, Fertility and Lactation)
- CYP2D6 ultra-rapid metabolisers (see section Special Warnings and Precautions for use)

Codeine is contraindicated in the event of impending childbirth or in case of risk of premature birth.

Special warnings and precautions for use
Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction.

To avoid risk of overdose
Check that paracetamol is absent from the composition of other medicinal products taken concomitantly.
Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).*

Severe cutaneous adverse reactions (SCARs): Life threatening cutaneous reactions Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop paracetamol treatment immediately and seek medical advice.

Paracetamol should be used upon medical advice in patients with:
- mild to moderate hepatocellular insufficiency (see Section Special warnings and precaution for use – Use in hepatic impairment)
- severe renal insufficiency (see Section Special warnings and precaution for use – Use in renal impairment)
- chronic alcohol use including recent cessation of alcohol intake
- low glutathione reserves
- Gilbert's syndrome

Codeine must be administered with caution in certain patients such as those who present with impaired cardiac, hepatic or renal function, hypotension, benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, gallbladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

Patients who have had a cholecystectomy should be treated with caution. The contraction of the sphincter of Oddi can cause symptoms resembling those of myocardial infarction or intensify the symptoms in patients with pancreatitis.

Codeine should be used with caution in patients with convulsive disorders.

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.

Monitoring after prolonged use should include blood count, liver function and renal function.
Codeine should only be used after careful risk-benefit assessment in case of:
- Opioid dependence
- Chronic constipation
- Conditions with elevated intracranial pressure and head trauma. Codeine can increase the pressure of cerebrospinal fluid and may increase the respiratory depressant effect. Like other narcotics, it causes adverse reactions that can obscure the clinical course of patients with head injury.
- Impaired consciousness
- Compromised respiratory function (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airway disease

Codeine should be used with caution in patients with CNS depression or decreased respiratory reserve.

Patients with known analgesic intolerance or known bronchial asthma must only use Panadeine after having consulted a physician (hypersensitivity reactions including bronchospasm possible).

<u>CYP2D6 metabolism</u>
Panadeine is contraindicated for use in patients who are CYP2D6 ultra-rapid metabolisers.

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.
However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing 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. Children are particularly susceptible due to their immature airway anatomy. Deaths have been reported in children with rapid metabolism who were given codeine for analgesia post adenotonsillectomy. Morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of rapid metaboliser mothers who take codeine. The prevalence of codeine ultra-rapid metabolism by CYP 2D6 in children is not known, but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers differs according to racial and ethnic group. It is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations. (See Section Special Warning and Precaution for use - Paediatric Use and Section Pregnancy and Lactation - Use in lactation.)

Hazardous and harmful use

Panadeine contains the opioid codeine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Panadeine at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed Panadeine.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse. See Section Special Warnings and Precautions for use – Paediatric use

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug. Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.
Patients should be advised not to share Panadeine with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Panadeine but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.
The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with hepatic and renal impairment (see Use in hepatic impairment and Use in renal impairment) and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients. The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Panadeine with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe Panadeine concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking Panadeine.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing Panadeine in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids).

Accidental ingestion/exposure

Accidental ingestion or exposure of Panadeine, especially by children, can result in a fatal overdose of codeine. Patients and their caregivers should be given information on safe storage and disposal of unused Panadeine (see section 6.4 Special precautions for storage and section Special precautions for disposal).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Use in hepatic impairment

Panadeine should be administered with caution to patients with hepatic dysfunction

Use in renal impairment

Panadeine should be administered with caution to patients with renal dysfunction.

Use in the elderly

Elderly people may be more sensitive to the effects of this medicinal product. The elderly are more likely to have hypertrophy, prostatic obstruction and age-related renal impairment and may be more susceptible to the undesirable effects due to opioid-induced urinary retention and the respiratory effects of opioid analgesics.

Paediatric use

Panadeine is contraindicated for use in children:

- younger than 12 years
- aged between 12-18 years
  in whom respiratory function might be compromised including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea.

Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism. (See section Special warnings and precaution for use – CYP2D6 metabolism)

Effects on laboratory tests

Uric acid and blood glucose: Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Interaction with other medicinal products and other forms of interaction
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 Panadeine 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 tranquillisers 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. (see Section Special Warnings and Precautions for Use)

The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Section Special warnings and Precautions for use).

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 (see Section Special warnings and Precautions for use).

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

Concomitant administration of Monoamine 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 antiperistaltic antidiarrhoeal drugs can increase the risk of severe constipation and CNS depression.

Morphinic agonists-antagonists – 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, an 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.

Fertility, Pregnancy and lactation

Effects on fertility

No data available

Use in Pregnancy

Category A

There are no indications of a connection between the occurrences of malformations in newborn infants and the use of paracetamol within the recommended dose range during the first four months of pregnancy. During pregnancy, however, the patient is requested to use Panadeine only after a thorough assessment of possible risks and benefits by the physician. If Panadeine is administered during pregnancy, morphinomimetic properties of codeine should be taken into account. Codeine may cause respiratory depression and withdrawal syndrome in neonates born to mothers who use codeine during the third trimester of pregnancy.
As a precautionary measure, use of Panadeine should be avoided during the third trimester of pregnancy and during labour.

Use in lactation
Panadeine is contraindicated during breast-feeding (see Section Contraindications and see also Section Special warnings and precautions for use - CYP2D6 metabolism) due to risk of respiratory depression in the infant). Paracetamol and Codeine is excreted into human breast milk. Analgesic doses excreted in breast milk are generally low.
However, infants of breastfeeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra rapid metaboliser of codeine. Codeine is excreted into human breast milk. Codeine is partially metabolized by cytochrome P450 2D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breast-fed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses (see Section Special warnings and precautions for use – CYP2D6 metabolism).

Therefore, Panadeine is contraindicated for use during breastfeeding. However, in circumstances where a breastfeeding mother requires codeine therapy, breastfeeding should be suspended and alternative arrangements should be made for feeding the infant for any period during codeine treatment. Breastfeeding mothers should be told how to recognise signs of high morphine levels in themselves and their babies. For example, in a mother, symptoms include extreme sleepiness and trouble caring for the baby. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties or limpness. Medical advice should be sought immediately.

Effects on ability to drive and use machines
Panadeine may cause drowsiness, disturbances of visuomotor coordination and visual acuity. Due to the 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.

Undesirable 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 refuted: 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, agranulocytosis 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 (see Section Warnings and precautions for use) 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 has been reported, as has pyroglutamic acidosis in patients with pre-disposing factors for glutathione depletion. Bronchospasm has 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. Other 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.

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.

<u>Symptoms</u>
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, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

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

<u>Treatment</u>

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 concentration of paracetamol 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 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and 100 mg/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 the severity, nature and course of clinical symptoms of intoxication and should follow standard intensive care protocols.

Pharmacodynamic properties
Pharmacotherapeutic group: Anilides, Paracetamol combinations
ATC Code: N02B E51

Mechanism of Action
Analgesic and antipyretic.
There is evidence to suggest that a combination of paracetamol with codeine is superior in analgesic action to either drug administered alone.

Clinical Trials

No data Available

Pharmacokinetic properties

Absorption

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine**;** peak plasma level occur *30*-12*0* 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 and norcodeine, which with codeine, are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours

Storage Condition

Store below 30^{o}C.

Expiry date

Do not use later than the date of expiry.

Presentation

Box contains 10 blisters x 20 tablets

Manufacturer

Sanofi India Limited
Plot No L-121, Phase III Verna Industrial Estate,
Goa, 403 722 India.

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