Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Syndol Film-coated Tablets Paracetamol 450 mg Codeine Phosphate Hemihydrate 10 mg Doxylamine succinate 5 mg Caffeine 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Paracetamol	450	mg
Codeine phosphate hemihydrate	10	mg
Doxylamine succinate	5	mg
Caffeine	30	mg

Excipients: contains lactose monohydrate and sunset yellow (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

Yellow, capsule shaped tablet, embossed 'SYNDOL' on one side with a single breakline on the reverse.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the short-term symptomatic reliefof tension headache and other pains of a similar tension state origin. For the symptomatic relief of pain following surgical and dental operations and procedures.

Syndol (which contains 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.

4.2 Posology and method of administration

Route of administration: Oral

Adults and children over 12 years:
Take 1 or 2 tablets every four or six hours as needed for relief.

Do not exceed 8 tablets per day.

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.

Do not take for more than 3 days continuously without medical review.

The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3 days.

Children under 12 years:
Syndol (which contains Codeine) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4)

Elderly

Dosage as for Adults
Codeine should be used with caution in elderly and debilitated patients, as they may be more susceptible to the respiratory depressant effects.

Renal impairment

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician.
See Table below:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic Impairment

In patients with impaired hepatic function or Gilbert's Syndrome, the dose must be reduced or the dosing interval prolonged. The daily dose of paracetamol should not exceed 2g/day unless directed by a physician.

The maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:
- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition'

4.3 Contraindications

Hypersensitivity to paracetamol, doxylamine, caffeine, codeine or other opioid analgesics, or any of the other ingredients listed in section 6.1.

Monoamine inhibitors (MAOIs) or within 14 days of stopping treatment. (See Section 4.5).

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

In women during breastfeeding (see section 4.6)

In children below 12 years of age

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)

Severe hepatocellular insufficiency

In the event of impending childbirth or in the case or premature birth

Conditions where morphine and opioids are contraindicated e.g.: acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure, following biliary tract surgery.

4.4 Special warnings and precautions for use

Syndol should be used upon medical advice in patients with:

- Mild to moderate hepatocellular insufficiency

- Severe renal insufficiency

- Chronic alcohol use including recent cessation of alcohol intake

- Low glutathione reserves

- Glucose-6-phosphate-dehydrogenase deficiency

- Gilberts syndrome

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 immediately Syndol treatment and seek medical advice.

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

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Syndol 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 and chronic obstructive airway disease

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

Use with caution in patients with convulsive disorders.

Monitoring after prolonged use should include blood count, liver function and renal function.

Syndol should be administered with caution in certain patients, such as those with impaired cardiac, hepatic or renal function, hypotension, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, prostatic hypertrophy, urinary retention, susceptibility to angle closure, shock, obstructive bowel disorders, acute abdominal conditions, recent gastrointestinal surgery, myasthenia gravis, a history of peptic ulcers or convulsions, patients with susceptibility to closed angle glaucoma, history of drug abuse or emotional instability, gallbladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

Elderly patients may be more sensitive to the effects of this medicinal product, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age-related kidney impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.
Codeine may induce faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction.
Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults.

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, they will not obtain adequate analgesic effects. 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, 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 prevalence of ultra-rapid metabolisers in different populations are summarised 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%

Risks from concomitant use of opioids and benzodiazepines:
Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression (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, and death. Concomitant use with alcohol is not recommended (see Section 4.5).

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.

The hazards of overdosage are greater in those with non-cirrhotic alcoholic liver diseases.

The use of this product may induce drowsiness. This product should not be used to sedate a child.

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.

Codeine, consumed in higher doses and over a prolonged period, may cause addiction.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence develop with prolonged use of high doses with withdrawal symptoms after sudden discontinuation of the drug such as restlessness and irritability. Cross-tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission). Administration must be discontinued gradually after prolonged treatments.

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.

Codeine can cause respiratory depression and withdrawal syndrome in newborns.

Caution is advised in patients with anxiety disorders (risk of enhancement) and arrhythmia (risk of tachycardia or extra systoles enhancement).

Excessive intake of caffeine should be avoided while taking this product.

Do not exceed the stated dose.

Do not take concurrently with any other paracetamol or codeine containing products.

Keep out of the reach and sight of children.

This product should only be used when clearly necessary.

If symptoms persist or become worse, consult your doctor.

Immediate medical advice should be sought in the event of overdosage, even if the patient feels well, because of the delayed risk of liver damage.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sunset yellow (E110). May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interactions

Paracetamol:

The rate of absorption of paracetamol may be increased by guaifenesin

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K (including coumarins). Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications during prolonged regular use, occasional doses have no significant effect.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as certain antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), monoamine oxidase inhibitors, tricyclic antidepressants, rifampicin and alcohol. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

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.

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.

Codeine:

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and phenothiazines. The hypotensive actions of diuretics and anti-hypertensive actions may be potentiated when used concurrently with opioid analgesics.

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

Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety agents or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression.

Concurrent use of hydroxyzine with codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation and CNS depression.

Concomitant use of codeine with a partial agonist or antagonist can precipitate or delay codeine effects.

Concomitant use of antimuscarinics or medications with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

The respiratory depressant effect caused by neurotransmitter blocking agents may be additive to the central respiratory depressant effects of opioid analgesics, CNS depression or excitation may occur if codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them.

Codeine may enhance the sedative effects of CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics and alcohol.

Codeine may have an additive muscarinic action with other drugs, such as atropine and some antidepressants.
Codeine should not be used in patients taking MAOI)s or within 14 days of stopping treatment as there is a risk of serotonin syndrome.

Quinidine can inhibit the analgesic effect of codeine.

Codeine may delay the absorption of mexiletene and thus reduce the antiarrhythmic effect of the latter. Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone. Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naloxone antagonise the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also block the therapeutic effect of opioids.

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.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

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 and Opioids:
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 4.4).

Alcohol and Opioids:
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 4.4).

Incompatabilities:

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 codeine phosphate 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 phosphatise, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies and with hepatobiliary imaging using technetium Te 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

Caffeine:
Caffeine reduces excretion of theophylline.

Caffeine may antagonise the sedative effects of other drugs.

The concomitant intake of gyrase inhibitors of the quinolone carbonic acid type (e.g., enoxacin, ciprofloxacin) can delay the elimination of caffeine and its degradation product paraxanthine.

CYP1A2 inhibitors (e.g., oral contraceptives, cimetidine, fluvoxamine, disulfiram, mexiletin) may reduce the caffeine metabolism in the liver.

Doxylamine Succinate:

CNS depressants: may enhance the sedative effects of CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics and alcohol.

Antimuscarinic drugs: may have an additive muscarinic action with other drugs, such as atropine and some antidepressants.

MAOIs: Not to be used in patients taking MAOIs or within 14 days of stopping treatment as there is a risk of serotonin syndrome.

4.6 Fertility, pregnancy and lactation

Syndol is not recommended during pregnancy.
Paracetamol
A large amount of data on the use of paracetamol in pregnancy indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Codeine can cause respiratory depression and withdrawal syndrome in newborns. Codeine crosses the placenta. There is no adequate evidence of safety in human pregnancy and a possible association with 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 analgesics during labour may cause respiratory depression in the neonate, especially the premature neonate. These agents should not be given during the delivery of a premature baby.

In animal studies it was found that prolonged intake of high amounts of caffeine may lead to spontaneous abortion or premature birth. Therefore women are advised to reduce their caffeine intake during pregnancy.

Lactation/Breastfeeding:

Syndol is contraindicated during breast-feeding.

Caffeine, codeine, doxylamine and paracetamol are excreted in 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.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

Caffeine ingested with breast milk may influence the condition and behaviour of the infant.

4.7 Effects on ability to drive and use machines

Syndol may cause drowsiness, disturbances of visuomotor coordination, visual acuity, and psychomotor impairment impacting the mental and/or physical ability required for the performance of potentially dangerous tasks, such as driving vehicles or using machines.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:	
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: frequency cannot be estimated from the available data	

Related to Paracetamol component

Blood and lymphatic system disorders
Very rare: thrombocytopenia, neutropenia, leucopenia
Not known: agranulocytosis, haemolytic anaemia, in particular in patients with underlying glucose-6-phosphate-dehydrogenase deficiency

Immune system disorders
Not Known: hypersensitivity such as anaphylactic shock, angioedema

Respiratory, thoracic and mediastinal disorders
Not known: bronchospasm (see section 4.4)

Skin and subcutaneous tissue disorders
Very rare: erythema, urticaria, rash
Not known: toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption (see section 4.4)

Hepatobiliary disorders
Not known: cytolytic hepatitis, which may lead to acute hepatic failure

Related to Codeine Component

Immune system disorders
Not known: hypersensitivity, allergic reactions (itch, skin rash, facial oedema)

Psychiatric disorders
Not known: confusional state, dysphoria, euphoria, hallucinations, nightmares, depression. Long term use also entails the risk of drug dependence.

Nervous system disorders
Not known: seizure, headache, somnolence, dizziness, sedation

Eye disorders
Not known: miosis, visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients

Ear and Labyrinth disorders
Not known: tinnitus, vertigo

Cardiac disorders
Not known: bradycardia, palpitations

Vascular disorders
Not known: hypotension/orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Not known: respiratory depression, dyspnoea

Gastrointestinal disorders
Very rare: pancreatitis
Not known: constipation, vomiting, nausea, dry mouth

Skin and subcutaneous tissue disorders
Not known: pruritus

Musculoskeletal and connective tissue disorders
Not known: muscle rigidity

Renal and urinary disorders
Not known: urinary retention, difficulties in micturition (dysuria, increased frequency, decrease in amount).

General disorders
Not known: fatigue, drowsiness, sweating, facial flushing, anorexia

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

Related to Doxylamine component

Nervous system disorders
Not known: paradoxical stimulation, psychomotor impairment, headache, drowsiness

Eye disorders
Not known: blurred vision

Blood and lymphatic system disorders
Not known: blood dyscrasias, thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis

Immune system disorders:
Not known: hypersensitivity, skin rash

Respiratory, thoracic and mediastinal disorders
Not known: thickened respiratory tract secretions

Gastrointestinal disorders
Not known: gastrointestinal disorders, dry mouth, acute pancreatitis

Renal and urinary disorders
Not known: urinary retention

Related to Caffeine Component

Psychiatric disorders
Not known: anxiety, insomnia, restlessness and tremor

Nervous system disorders
Common: headache, mild delirium

Gastrointestinal disorders
Not known: gastric disorders, nausea, vomiting

Cardiac disorders
Not known: heart rate increased

Large doses may cause restlessness, excitement, muscle tremor, tinnitus, scintillating scotoma, tachycardia and extrasystoles. Caffeine increases gastric irritation and may cause gastric ulceration.

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 the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Paracetamol overdose

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, disseminated intravascular coagulation 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:

While the dose of Codeine Phosphate hemihydrate in this preparation is relatively small and therefore less likely to prove a problem, the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Symptoms of over-dosage include central nervous system depression and/or respiratory depression may develop but are 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.

The ingestion of very high doses 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.

Management:
This should include symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Intensive support therapy may be required to correct respiratory failure and shock. 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-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. A dose of 0.4-2 mg is given intravenously or intramuscularly to adults, this is repeated at intervals of 2-3 minutes; if necessary up to 10mg of naloxone may be given. In children doses of 5-10µg/kg body weight may be given intravenously or intramuscularly. Codeine is dialysable.

Doxylamine:
In evaluation of cases of intoxication with doxylamine, no correlation was found between the amount ingested or plasma concentration and the frequency or extent of symptoms. The most common symptom was impaired conciousness. Psychotic behaviour, seizures, and antimuscarinic symptoms such as tacycardia and mydriasis were also seen. Rhabdomyolosis had been noted in cases of doxylamine overdosage, with an associated rise in plasma creatine kinase and myoglobinuria, and suggested that doxylamine has a direct effect on striated muscle.

Management
If clinical syptoms of doxylamine succinate overdose are suspected, consult a doctor or the NPIS immediately. Rhabdomyolysis and secondary acute renal failure are rare but potentially serious complications, making early recognition and treatment essential. Treatment of rhabdomyolysis induced by doxylamine overdose is by aggressive hydration and urine alkalisation. Aggressive hydration with intravenous crystalloids such as 0.9% saline (NS) or lactated Ringer's solution (LR) at a rate of 300 – 500 ml/h in an adult is essential. To date, it has been believed that there is no difference in effectiveness between NS and LR.

Caffeine:
Symptoms of toxicity can occur at caffeine doses of 1 g and above (15 mg/kg if body weight is below 70 kg) if the dose is taken over a short period.
Early symptoms with acute caffeine poisoning are usually tremor and restlessness. These are followed by nausea, vomiting, tachycardia and confusion. With serious intoxication, delirium, seizures, tachycardia and arrhythmias, hypokalaemia and hyperglycaemia may occur.

Fatal poisoning is rare. If symptoms become apparent or overdose is suspected, consult a doctor immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02A J06

Paracetamol has analgesic and antipyretic properties. Codeine phosphate hemihydrate is an analgesic. Doxylamine succinate is an antihistamine and caffeine is a mild stimulant.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through microgram 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 hemihydrate and caffeine are widely published. Doxylamine succinate is readily absorbed from the gastrointestinal tract.Following oral administration the effects start with 15 to 30 minutes and peak within 1 hour. In humans 60-80% of doxylamine has been recovered in urine at 24 hours post-dose.

5.3 Preclinical safety data

Paracetamol:
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

Maize starch
Croscarmellose sodium
Povidone
Talc
Magnesium stearate
Opadry II yellow (lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol 4000, quinoline yellow (E104), FD&C yellow/sunset yellow (E110)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special storage precautions.

6.5 Nature and contents of container

Laminate blister tray consisting of opaque, white 250 micron PVC, heat-sealed to 20 micron child resistant aluminium foil. The blisters are packed in cardboard cartons.

Pack sizes: 4, 10, 20, 24 and 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/175/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd September 1975
Date of last renewal: 17th April 2009

10 DATE OF REVISION OF THE TEXT

April 2020