Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Syndol Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol	450mg
Codeine Phosphate Hemihydrate	10mg
Doxylamine Succinate	5mg
Caffeine	30mg

Excipients-Contains Lactose Monohydrate and Sunset Yellow Aluminium Lake (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Product imported from the UK:
Yellow, capsule shaped tablet, embossed 'SYNDOL' on one side with a single breakline on 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 relief of tension headache and other pains of a similar tension state origin. For the symptomatic relief of pain following surgical and dental operations and procedures.

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.
Not recommended for children under 12 years.
Do not exceed 8 tablets per day.
Do not take for more than 3 days continuously without medical review.

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 and Hepatic Impairment
Care is advised in the administration of paracetamol-containing product to patients with severe renal or severe hepatic impairment and in those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with alcoholic liver disease. Patients suffering from liver or kidney disease should take paracetamol under medical supervision. The dosage in renal and hepatic impairment must be reduced.

4.3 Contraindications

Hypersensitivity to paracetamol, codeine or other opioid analgesics, or any of the other constituents in the product.
Monoamine inhibitors (MAOIs) or within 14 days of stopping treatment. (See Section 4.5).
Use of codeine containing products is contraindicated in mothers who are breast-feeding unless prescribed by a doctor.

4.4 Special warnings and precautions for use

Do not exceed the stated dose.
Do not take concurrently with any other paracetamol or codeine containing products.
Keep out of the sight and reach of children.

Care is advised in the administration of this product to patients with impaired kidney or liver function and in those with hypertension, hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, urinary retention, susceptibility to angle closure, shock, obstructive bowel disorders, acute abdominal conditions, recent gastrointestinal surgery, gallstones, myasthenia gravis, a history of peptic ulcers or convulsions, and also in patients with susceptibility to closed angle glaucoma or a history of drug abuse or emotional instability.

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.

Codeine is partially metabolised by CYP2D6. 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 ultra-rapid metaboliser there is an increased risk of developing side-effects of opioid toxicity, including nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates include that up to 1 to 2% of the Caucasian population may be ultra-rapid metabolisers.

The hazards of overdosage are greater in those with non-cirrhotic alcoholic liver disease.
The use of this product may induce drowsiness. This product should not be used to sedate a child.
Alcoholic drink should be avoided.
Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped.
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 aluminium lake (E110). May cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Alcoholic drink should be avoided.

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.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Medicinal products which induce hepatic microsomal enzymes, such as alcohol, barbiturates, monoamine oxidase inhibitors and tricyclic
antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdose.

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 hypertensive actions may be potentiated when used concurrently with opioid analgesics.

Concurrent use of hydroxizine 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 constipations.
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 monooxamine oxidase inhibitors, or within two weeks of stopping treatment with them.

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

Syndol may have an additive muscarinic action with other drugs, such as atropine and some antidepressants.
Syndol should not be used in patients taking monoamine oxidase inhibitors (MAOIs) 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 letter. Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domeridone. 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.

Incompatabilities: Codeine has been reported to be incompatible with phenobarbitone sodium forming a codeinephenobarbitone 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 undergoes extensive metabolism by hepatic microsomal cytochrome P450, factors known to alter the activity of this enzyme system may influence caffeine clearance. Thus, caffeine elimination is enhance in cigarette smokers and inhibited by cimetidine, disulfiram and oral contraceptive steroids.

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

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.
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.

Lactation/Breastfeeding:
Paracetamol:
Paracetamol is excreted in breast milk but not in clinically significant amounts. Available published data do not contraindicate breast feeding.

Codeine:
At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and are unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of codeine the active metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant. 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:
Caffeine is excreted in breast milk but at levels which are not thought to present a hazard, although irritability and a poor sleeping pattern have been reported.

4.7 Effects on ability to drive and use machines

Caution is advised as this medicine may lead to drowsiness and impaired concentration aggravated by simultaneous intake of alcohol or other central nervous system depressant agents.

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.	

Paracetamol
Rare (≥1/10,000 to < 1/1,000)
Hypersensitivity skin rash, blood dyscrasias including Thrombocytopaenia, leucopenia, pancytopaenia, Neutropaenia and agranulocytosis, acute pancreatitis.

Codeine Phosphate
Unknown Constipation, Drowsiness

Unknown Nausea, vomiting, sweating, facial flushing, dry mouth, blurred or double vision, dizziness, Orthostatic hypotension, malaise, tiredness, Headache, anorexia, vertigo, bradycardia, Palpitations, respiratory depression, dyspnoea, Allergic reactions (itch, skin rash, facial oedema) and difficulties in micturition (dysuria, increased frequency, decrease in amount.)

Rare (≥1/10,000 to < 1/1,000)
Convulsions, hallucinations, nightmares, uncontrolled muscle movements, muscle rigidity, mental depression and stomach cramps. 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.

Doxylamine succinate
Common (≥1/100 to <1/10)
CNS effects: Drowsiness (usually diminishes within a few days), paradoxical stimulation, headache, psychomotor impairment.
Antimuscarinic effects: Urinary retention, dry mouth, blurred vision, gastrointestinal disturbances, thickened respiratory tract secretions.
Rare (≥1/10,000 to < 1/1,000)
Hypersensitivity, skin rash, blood dyscrasias, Thrombocytopenia, leucopenia, pancytopenia, Neutropenia and agranulocytosis, acute pancreatitis.

Caffeine
Common (≥1/100 to <1/10)
CNS effects: insomnia, headache, restlessness, nervousness and mild delirium.
GI effects: nausea, vomiting and gastric irritation.
Large doses may cause restlessness, excitement, muscle tremor, tinnitus, scintillating scotoma, tachycardia and extrasystoles. Caffeine increase gastric irritation and may cause gastric ulceration.

4.9 Overdose

Paracetamol:
There may be no initial symptoms following overdose.

Symptoms of over-dosage in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by gluthathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Risk factors:
A–If the patient is on long term treatment with carbamazepine, Phenobarbital, phenytoin, primidone, rifampicin, St Johns Wort or other drugs that induce liver enzymes.

Or

b- Regularly consumes ethanol in excess of recommended amounts.

Or

c-Is likely to be glutathione deplete e.g eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Management:
Immediate treatment is essential in the management of a paracetamol overdose. Despite a lack of significant early

symptoms, patients should be referred to hospital urgently for immediate medical attention.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

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.

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 competive 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:
The most commonly reported adverse effects following dosing with caffeine are GI irritation and CNS stimulation. Adverse CHS effects include insomnia, restlessness, nervousness and mild delirium; adverse GI effects include nausea, vomiting and gastric irritation.
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: N02B E51

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

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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn Starch
Povidone
Talc
Magnesium Stearate
Croscarmellose Sodium
Hyprmellose
Polyethylene Glycol 400
Quinoline yellow aliuminium lake (E104)
Sunset Yellow aluminium lake (E110)
Titanium Dioxide (E171)
Lactose Monohydrate
Polyethylene Glycol 4000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Blister strips in an overlabelled outer container
Pack size: 20

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 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/111/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd July 2009

10 DATE OF REVISION OF THE TEXT

October 2013