SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Syndol Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 450.00mg

Codeine Phosphate 10.00mg

Doxylamine Succinate 5.00mg

Caffeine 30.00mg

Also contains E110 (sunset yellow), E104 (quinoline yellow) and lactose monohydrate

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet (Tablet)

A yellow film coated tablet embossed “SYNDOL” on one side, with a break line on the underside.

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 treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone such as headache, tension headache,

migraine, neuralgia, toothache, dysmenorrhoea, muscular and rheumatic aches and pains and post-operative analgesia following surgical or dental procedures.

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

Posology

Treatment goals and discontinuation

Before initiating treatment with Syndol, treatment duration and treatment goals should be agreed together with the patient, in accordance with pain management guidelines.

Duration of treatment

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician. Do not take continuously for more than 3 days without consulting your doctor.

The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

Adults

One or two tablets every four to six hours as needed for relief. Total dosage over a 24 hour period should not normally exceed eight tablets.

Elderly and debilitated

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

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 (see sections 4.3 and 4.4).

Children aged 16 years to 18 years

One to two tablets every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Children aged 12 years to 15 years

One tablet every six hours when necessary to a maximum of 4 tablets in 24 hours

Method of administration

Oral use.

4.3 Contraindications

Hypersensitivity to paracetamol, codeine or other opioid analgesics, doxylamine succinate, caffeine, or any of the other constituents.
Due to interaction with the doxylamine succinate component, the concomitant use of Syndol with monoamine inhibitors (MAOIs) or within 14 days of stopping treatment with these medicines is contraindicated, as there is a risk of serotonin syndrome (see section 4.5).

Conditions where morphine and opioids are contraindicated e.g:

- Acute asthma (during an attack)
- Acute respiratory depression and in chronic obstructive pulmonary disease
- Acute alcoholism
- Head injuries
- Raised intra-cranial pressure
- Following biliary tract surgery
- Risk of paralytic ileus
- Breast-feeding (see Section 4.6)
- Respiratory insufficiency
- In the event of impending childbirth or in case of risk of premature birth
- 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).

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

Severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Paediatric population

Not recommended for children under 12 years of age.

CY2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid 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.

Codeine is not recommended in children 12 to 18 years of age with risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as obstructive sleep apnea, obesity, and pulmonary disease.

Do not exceed the stated dose.

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

This product may cause drowsiness.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Syndol. Repeated use of Syndol can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Syndol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.

For patients who experience signs and symptoms of OUD, and/or exibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

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.

Excessive intake of caffeine (products with caffeine e.g. coffee, tea, foods, other drugs and beverages) should be avoided while taking this product.

Keep out of the reach and sight of children.

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

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

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 Syndol. 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 immediately stop Syndol

treatment and seek medical advice.

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.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. See also Section 4.3 regarding contraindication of taking Syndol with MAOIs because of the doxylamine component.

Syndol must be administered with caution in certain patients, such as those with hypotension.

Syndol must be administered with caution in certain patients, such as those who present impaired cardiac, hepatic or renal function, 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.

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of opioids, including codeine, and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of sedative medicines, such as benzodiazepines or related drugs, with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe codeine concomitantly with sedative medicines such as benzodiazepines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Caution is advised in patients with:

- Anxiety disorders (risk of enhancement).

- Arrhythmia (risk of tachycardia or extra systoles enhancement).

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
- Gilbert´s syndrome

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 (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airway disease.

Elderly people 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.

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).

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

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

Co-administration of enzyme-inducing antiepileptic medications may increase toxicity; doses should be reduced.

E110 (sunset yellow) and E104 (quinoline yellow) may cause allergic reactions.

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

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

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.

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated**.**

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

The label will state:

Front of Pack:

- Can cause addiction
- For three days use

only

Back of Pack:

- For the short term treatment of acute moderate pain where other

painkillers have not worked. Do not take less than four hours after taking other pain killers. This medicine is used for tension headaches, migraines, muscular pains and tension.

- Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
- Do not take anything else containing paracetamol whilst taking this medicine.
- Talk to your doctor at once if you take too much of this medicine, even if you feel well.
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

Important things you should know about Syndol

- This medicine can only be used for the short term treatment of acute moderate pain where other painkillers have not worked.
- You should only take this product for a maximum of three days at a

time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.

Section 1: What Syndol is and what it is used for

- Syndol is used for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen and aspirin alone such as headache, including muscle contraction or tension headache, migraine, neuralgia, period pain, toothache and other dental pain, muscular and rheumatic aches and pains and for pain relief following surgery or dental procedures.

Section 2: What you need to know before you take Syndol

- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.
- Do not take Syndol if you know that you metabolise very rapidly codeine into morphine.

(In the "Pregnancy and breast-feeding" subsection)

If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take Syndol whilst breastfeeding. Codeine and morphine passes into the breast milk.

Section 3: How to take Syndol

- Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist.
- This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get

withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

Section 4: Possible Side effects

- Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

- How do I know if I am addicted?

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time.
- You need to take more than the recommended dose.

When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

The anticoagulant effect of warfarin and other antivitamin K may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

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), rifampicin and alcohol. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

Syndol may enhance the sedative effects of CNS depressants such as alcohol, barbiturates, anaesthetics, hypnotics, other opioid analgesics, anxiolytic sedatives, antipsychotics, tricyclic antidepressants and phenothiazines, resulting in increased CNS depression. It may also have an additive antimuscarinic action with other drugs, such as atropine and some 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.

<u>Benzodiazepines</u>
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of

concomitant use should be limited (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).

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 enzymeCYP2D6 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.

Caffeine may antagonise the sedative effect of other drugs (e.g. barbiturates, anti-histaminics).

Caffeine reduces excretion of theophylline.

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.

The hypotensive actions of diuretics and anti-hypertensive agents may be potentiated when used concurrently with opioid analgesics. Concurrent use of hydroxyzine with codeine may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Quinidine can inhibit the analgesic effect of codeine.

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 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.

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

Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Doxylamine: Monamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with these products as there is a risk of serotonin syndrome (see section 4.3).

Concomitant administration of pethidine and possibly other opioid analgesics to patients taking MAOIs has been associated with very severe and sometimes fatal reactions such as severe CNS excitation or depression, including hypertension or hypotension. Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Incompatibilities: 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 phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

The metabolism of paracetamol is possibly accelerated by carbamazepine, phenytoin, phenobarbital, primidone (also there have been isolated reports of hepatotoxicity).

Concomitant use of Syndol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If

clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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 analgesia 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.

The prolonged intake of high amounts of caffeine may lead to spontaneous abortion or premature birth in pregnant women.
Non-clinical studies have shown reproductive toxicity at very high doses.
Codeine can cause respiratory depression and withdrawal syndrome in newborns.

Because of the content of caffeine and codeine, Syndol is not recommended during pregnancy.

Breastfeeding

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Codeine should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites 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.

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

Syndol is contraindicated during breast-feeding.

4.7 Effects on ability to drive and use machines

Some side effects related to doxylamine succinate include drowsiness (usually diminishes within a few days), paradoxical stimulation, headaches, psychomotor impairment, hypotension, dizziness, confusion, tremor and convulsions.

Opioid analgesics can impair mental function and cause blurred vision and dizziness. Rare side effects may include convulsions, hallucinations, blurred or double vision, dizziness and orthostatic hypotension

These side effects may have a noticeable impact on the ability to driving and operate machinery. Patients should ensure they are not affected before driving or operating machinery.

See section 4.8 for more information on side effects.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse effects of doxylamine succinate:

Common side effects:

CNS effects: Drowsiness (usually diminishes within a few days), paradoxical stimulation, headaches, psychomotor impairment.

Antimuscarinic effects: Urinary retention, dry mouth, blurred vision, gastrointestinal disturbances, thickened respiratory tract secretions.

Rare side effects:

Hypotension, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmia hypersensitivity reactions, blood disorders and liver dysfunction.

Adverse effects of paracetamol:

Blood and lymphatic system disorders
Very rare: thrombocytopenia, neutropenia, leukopenia.
Not known: agranulocytosis, haemolytic anaemia in particular in patients with underlying

glucose 6-phosphate-dehydrogenase deficiency.

Immune system disorders
Hypersensitivity including skin rash may occur.
Not known: Anaphylactic shock, angioedema.

Skin and subcutaneous tissue disorders
Very rare cases of serious skin reactions have been reported.
Very rare: erythema, urticaria, rash.
Not known: toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption.

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

Respiratory, thoracic and mediastinal disorders

Not known: Bronchospasm

Metabolism and nutrition disorders
High anion gap metabolic acidosis, frequency – not known.

Description of selected adverse reactions

High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4).
Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Adverse effects of Codeine:

The most frequent undesirable effects of codeine are constipation and drowsiness. Less frequent effects are 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). Side effects, which occur rarely, include convulsions, hallucinations, nightmares, uncontrolled muscle movements, muscle rigidity, mental depression and stomach cramps. Very rare cases of pancreatitis have been reported.

Immune system disorders
Not Known: hypersensitivity.

Psychiatric disorders
Not Known: confusional state, dysphoria, euphoria. 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.
Not Known: 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.

Skin and subcutaneous tissue disorders
Not Known: pruritus.

Renal and urinary disorders
Not Known: urinary retention.

Vascular disorders
Not Known: Hypotension.

Hepatobiliary disorders
Not known: sphincter of Oddi dysfunction

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.

Drug dependence

Repeated use of Syndol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Adverse effects of Caffeine:

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

Gastrointestinal disorders

Not known: gastric disorders.

Cardiac disorders
Not known: heart rate increased.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

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 (see below).

Risk Factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's 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.

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

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin may occur and the INR may increase. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death.

It can also lead to pancreatitis, acute renal failure and pancytopenia.

Management

Treatment involves gastric aspiration and lavage, preferably within 4 hours of ingestion.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

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 24h from ingestion should be discussed with the NPIS or a liver unit.

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

Effects on laboratory values
Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Codeine

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

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.

Symptoms

Central nervous system depression, including respiratory depression, may develop but is 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 general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. 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.

Caffeine

Symptoms

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol - analgesic, antipyretic

Codeine Phosphate - analgesic

Doxylamine Succinate - antihistamine

Caffeine - mild stimulant

Pharmacotherapeutic group: Anilides, Paracetamol combinations

ATC Code: NO2B E51

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

The pharmacokinetics of paracetamol, codeine phosphate and caffeine are widely published (see Goodman and Gilman's Pharmacological Basis of Therapeutics, Seventh Edition pgs. 693, 505 and 596 respectively. Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration the effects start within 15 to 30 minutes and peak within one hour. In humans 60 - 80% of doxylamine given has been recovered in urine at 24 hours post-dose.

The bioavailabilities of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately.

Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide.Minor routes of metabolism include O- demethylation leading to morphine, N-demethylation to norcodeine and both O- and N-demethylation to normorphine. Morphine and norcodeine are further transformed to glucuronide conjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h (84.4±15.9%).

The O-demethylation of codeine to morphine is catalyzed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine.

Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes

5.3 Preclinical safety data

None stated

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

Povidone

Croscarmellose Sodium

Pregelatinised Maize Starch

Magnesium Stearate

Talc

Purified Water

Opadry II Yellow (lactose monohydrate, titanium dioxide, hypromellose, quinoline yellow (E104), sunset yellow (E110) and polyethylene glycol 4000)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C in the original packaging to protect from moisture.

6.5 Nature and contents of container

Blister strips: 250 micron PVC and aluminium foil 20 micron coated with a 15 micron PVC layer

Blister strips are presented in cardboard cartons. Pack sizes are 4*, 10, 20, 30 tablets (*sample pack)

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs Unlimited Company,

Suite 12, Bunkilla Plaza,

Bracetown Business Park,

Clonee,

Co. Meath,

Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 35104/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/01/1999 / 27/02/2009

10 DATE OF REVISION OF THE TEXT

10/04/2026