

Public Assessment Report
Decentralised Procedure

CODIPAR 15MG/500MG EFFERVESCENT TABLETS
ZAPAIN 30MG/500MG EFFERVESCENT TABLETS
(PARACETAMOL AND CODEINE PHOSPHATE)

UK/H/1866 and 3322/001/DC
UK Licence No: PL 12762/0405 and 0412

GOLDSHIELD PHARMACEUTICALS LIMITED

LAY SUMMARY

On 16th August 2010, the UK granted Goldshield Pharmaceuticals Limited Marketing Authorisations (licences) for Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets (PL 12762/0405 and 0412; UK/H/1866 and 3322/001/DC). These are prescription-only medicines (POM) for the relief of mild to severe short term pain.

The active ingredients in this medicine are paracetamol and codeine. Paracetamol is an analgesic, which relieves pain, and an antipyretic, which lowers raised temperatures. Codeine is a painkiller.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets outweigh the risks; hence these Marketing Authorisations have been granted.

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Module 6: Steps taken after initial procedure	Not applicable

Module 1

Product Name	Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets
Type of Application	Well established use application, Article 10.3
Active Substance	Paracetamol and Codeine Phosphate
Form	Effervescent Tablets
Strength	15mg/500mg and 30mg/500mg
MA Holder	Goldsheild Pharmaceuticals Limited NLA Tower 12-16 Addiscombe Road Croydon CR0 0XT UK
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Ireland
Procedure Number	UK/H/1866 and 3322/001/DC
End of Procedure	Day 215 – 12 th July 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codipar 15mg/500mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Codeine Phosphate hemihydrate 15mg and Paracetamol 500mg.
Excipients: Each tablet also contains 389mg of sorbitol and 379 mg of sodium.
For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet
Bevelled, flat, round, white tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of mild to severe acute pain

4.2 Posology and method of administration

Method of administration: Oral

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

Adults: The usual dose is two tablets every four hours as required. The total daily dose should not exceed 4 g paracetamol (8 tablets in a day).

Elderly: As for adults, however a reduced dose may be required (see section 4.4)

Paediatric population: Not recommended in children below the age of 18 years (see section 5.1).

4.3 Contraindications

Hypersensitivity to either paracetamol or codeine, or any of the excipients of Codipar tablets.
Conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or within 14 days.

Codipar is also contraindicated in severe liver disease and severe renal impairment. The hazards of overdose could be greater in those with alcoholic liver disease.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor (see section 4.6).

4.4 Special warnings and precautions for use

Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy / urethral stricture and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated, since side effects are more frequent and may lead to intolerance of the product with regular, long-term use.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Drug dependence of the morphine type can be produced by codeine, and the potential for drug abuse with codeine must be considered. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

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.

Care should be taken in patients with liver and kidney disease with suitable dose reductions as appropriate.

Prolonged use except on the doctor's advice may be harmful.

This product should be used only when clearly necessary.

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

Patients must be advised not to exceed the recommended dose and not to take other paracetamol containing products concurrently.

The risk-benefit of continued use should be assessed regularly by the prescriber.

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking Codipar, and to consult their doctor if symptoms persist.

The cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

As the effervescent tablet contains 389mg of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine

This medicine contains 379 mg sodium in each tablet. This should be taken into consideration by patients on a controlled sodium (salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine. The CNS depressant action of Codipar may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Codipar and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and coadministration with an antimuscarinic drug may cause urinary retention.

The absorption of paracetamol may be enhanced by metoclopramide or domperidone, and absorption may be reduced by cholestyramine.

The metabolism of paracetamol is increased in patients taking enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be increased by long term regular daily use of paracetamol, with increased risk of bleeding. Occasional doses of paracetamol do not have a significant effect on these anticoagulants.

Dependence of codeine hypoalgesia on morphine formation via CYP2D6 makes this effect liable to interaction with drugs that are inhibitors of CYP2D6. Examples of potent inhibitors of CYP2D6 are quinidine, some selective serotonin reuptake inhibitors, some neuroleptics and ritonavir.

Codeine may delay the absorption of mexilitine

4.6 Pregnancy and lactation

Pregnancy: On the basis of published literature (Danish National Birth Cohort), paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months.

Use of codeine during pregnancy may lead to withdrawal symptoms in neonates, and use during labour may cause neonatal respiratory depression.

Codipar is then not recommended during pregnancy.

Lactation: Codeine is excreted in the human milk. The decision to use codeine in nursing women should be based on clinical judgment. If used in such patients, codeine should be administered in the lowest effective dosage for the shortest possible time.

In nursing mothers, who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia, miosis and difficulty breastfeeding or breathing. In severe cases respiratory depression and death can occur. In severe cases, naloxone may be appropriate to reverse the effects. The lowest effective dose should be used, for the shortest possible time.

Nursing mothers should be informed about carefully monitoring the infant during treatment for any signs and/or symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breastfeeding, breathing difficulties, miosis and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed. The nursing mother should be informed about monitoring for signs and symptoms of maternal opioid toxicity as well. Should such signs/symptoms be noted in mother or baby, the mother should immediately stop taking all codeine-containing medicines and seek medical advice.

Paracetamol is distributed in human milk, although its concentration is 20% lower than in plasma. For these reasons, Codipar should be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if Codipar causes dizziness or sedation. Codeine may cause visual disturbances.

4.8 Undesirable effects

Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.

The most commonly (>1/100, <1/10) reported reactions are:

Central nervous system:	Dizziness Light-headedness Sedation Headache
Gastro-Intestinal:	Nausea & vomiting Constipation Abdominal pain
Psychiatric:	Dysphoria Euphoria
Respiratory:	Shortness of breath
Skin:	Pruritus Rash Urticaria

In clinical use of paracetamol-containing products, blood dyscrasias (including thrombocytopenia and agranulocytosis) are reported rarely (>1/10000, <1/1000).

Also, rarely hypersensitivity including skin rash may occur with paracetamol use. _

The frequencies of the following side effects are not known or cannot be estimated from the data available:

<u>Eye disorders:</u>	Miosis
<u>Renal and urinary disorders:</u>	Urinary retention

Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

4.9 Overdose

Codeine

Large doses of codeine produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur from respiratory failure. Blood concentrations of codeine ranged from 1.4 to 5.6 mg/l in eight adults whose deaths were attributed primarily to codeine overdosage.

Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and the institution of controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Opioid antagonists may be employed. Gastric lavage should be considered. Patients should remain under observation, as per hospital guidelines and on a case per case basis.

Paracetamol

Because of its ready availability, paracetamol is often taken in overdosage. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested. The major complication is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (plasma aminotransferase > 1000 mg/l). About 1% develop fulminant hepatic failure which is usually fatal. Renal failure from acute tubular necrosis is a further uncommon complication which may develop in the absence of hepatic failure. There are no specific early manifestations of severe paracetamol poisoning. Consciousness is not impaired except in the occasional unusually severely poisoned patient with metabolic acidosis, and maximum abnormality of liver function tests is delayed for at least 3 days.

Emergency estimation of the plasma paracetamol concentration is therefore necessary to determine the severity of intoxication and the need for specific therapy with N-acetylcysteine (NAC).

Patients who have ingested more than 150 mg/kg should have gastric lavage performed if they present within an hour of ingestion. Activated charcoal may also be given. A plasma paracetamol level will indicate the likelihood of a patient developing high ALT/AST activities (i.e. > 1,000 i.u. /L) and must be measured at least 4 hours after ingestion. Plasma levels measured less than 4 hours post-ingestion cannot be interpreted. Patients with a plasma level above the treatment line require N-acetylcysteine (NAC). A paracetamol normogram should be employed to determine treatment levels.

Patients who present to an Accident and Emergency Department more than 8 hours after ingesting a paracetamol overdose are at greater risk of developing hepatic damage. In cases of severe poisoning, hepatic failure may progress to encephalopathy, coma and death.

Blood should be taken for a plasma level, but the NAC infusion should be started as soon as possible if more than 150 mg/kg was taken. The NAC infusion should not be delayed while awaiting the result of the plasma paracetamol level. Administration of the antidote should be stopped if the plasma level is subsequently found to be below the treatment line. General supportive measures must be available. At the end of the NAC infusion, blood should be taken to check the INR and creatinine concentration. If the investigations are abnormal, a further infusion of NAC (at 16 hour dose), to be continued until recovery or death, should be considered.

In the range of concentrations associated with overdosage, paracetamol may give a false positive result for plasma salicylate in tests based on the direct colour reaction with ferric ions. In the same circumstances it may induce spuriously high results for blood dextrose estimated with the YSI and Yellow Springs Model 23AM dextrose analyzers. Conversely, it may cause falsely low results for dextrose when the dextrose peroxidase/dextrose-6-phosphate dehydrogenase method is used

Liver damage following overdosage is relatively uncommon in young children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. Paracetamol is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily. The inhibitory effect of paracetamol on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function. Animal studies have indicated that paracetamol strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions).

Codeine is a centrally acting analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has an exceptionally low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. However, its antitussive actions may involve distinct receptors that bind codeine itself.

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic for about 10% of the Caucasian population.

The fixed combination of paracetamol and codeine has been shown to be effective in acute nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 min and 2 h after ingestion. Paracetamol is distributed throughout most body tissues, with an apparent volume of distribution of approximately 1 L/kg of body weight. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta. Paracetamol is extensively metabolised in the liver and the total body clearance is about 5 ml/min/1/kg. Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine.

Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 h and the plasma half-life is about 3.5 h. The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine crosses the placenta and is present in the milk of lactating mothers.

Codeine is metabolised in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), and other metabolites. After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h.

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

5.3 Preclinical safety data

There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Sorbitol Neosorb P60 W
Povidone K30
Sodium Saccharin
Macrogol 6000

Grapefruit flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Strips of Aluminium / polyethylene foils

Each strip contains 4 tablets individually packed in cardboard containers of 100 tablets.

6.6 Special precautions for disposal and other handling

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd
NLA Tower 12-16 Addiscombe Road
Croydon CR0 0XT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0405

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/08/2010

10 DATE OF REVISION OF THE TEXT

16/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Zapain 30mg/500mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Codeine Phosphate hemihydrate 30mg and Paracetamol 500mg.
Excipients: Each tablet also contains 487mg of sorbitol and 413 mg of sodium.
For a full list of excipients see 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet
Bevelled, flat, round, white tablet with a score line on one face
Although Zapain tablets have a score line the tablets are not to be halved as they do not divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of mild to severe acute pain.

4.2 Posology and method of administration

Method of administration: Oral

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

Adults: The usual dose is one or two tablets every four hours as required. The total daily dose should not exceed 4 g paracetamol (8 tablets in a day).

Elderly: As for adults, however a reduced dose may be required (see section 4.4)

Paediatric population: Not recommended in children below the age of 18 years (see section 5.1).

4.3 Contraindications

Hypersensitivity to either paracetamol or codeine, or any of the excipients of Zapain tablets.
Conditions where morphine and opioids are contraindicated e.g., acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery; monoamine oxidase inhibitor therapy, concurrent or within 14 days.

Zapain is also contraindicated in severe liver disease and severe renal impairment. The hazards of overdose could be greater in those with alcoholic liver disease.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor (see section 4.6).

4.4 Special warnings and precautions for use

Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy / urethral stricture and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated, since side effects are more frequent and may lead to intolerance of the product with regular, long-term use.

Codeine at high doses has the same disadvantages as morphine, including respiratory depression. Drug dependence of the morphine type can be produced by the Codeine, and the potential for drug abuse with codeine must be considered. Codeine may impair mental or physical abilities required in the performance of potentially hazardous tasks.

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.

Care should be taken in patients with liver and kidney disease with suitable dose reductions as appropriate.

Prolonged use except on the doctor's advice may be harmful.

This product should be used only when clearly necessary.

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

Patients must be advised not to exceed the recommended dose and not to take other paracetamol containing products concurrently.

The risk-benefit of continued use should be assessed regularly by the prescriber.

Patients must be advised not to take other products containing paracetamol or opiate derivatives when taking Zapain, and to consult their doctor if symptoms persist.

The cough suppressant effect of codeine may be undesirable in patients with some respiratory conditions.

As the effervescent tablet contains 487mg of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine

This medicine contains 413 mg sodium in each tablet. This should be taken into consideration by patients on a controlled sodium (salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.

The CNS depressant action of Zapain may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Concomitant administration of Zapain and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and coadministration with an antimuscarinic drug may cause urinary retention.

The absorption of paracetamol may be enhanced by metoclopramide or domperidone, and absorption may be reduced by colestyramine.

The metabolism of paracetamol is increased in patients taking enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol.

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Dependence of codeine hypoalgesia on morphine formation via CYP2D6 makes this effect liable to interaction with drugs that are inhibitors of CYP2D6. Examples of potent inhibitors of CYP2D6 are quinidine, some selective serotonin reuptake inhibitors, some neuroleptics and ritonavir.

Codeine may delay the absorption of mexilitine

4.6 Pregnancy and lactation

Pregnancy: On the basis of published literature (Danish National Birth Cohort), paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months.

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Lactation: Codeine is excreted in the human milk. The decision to use codeine in nursing women should be based on clinical judgment. If used in such patients, codeine should be administered in the lowest effective dosage for the shortest possible time.

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Paracetamol is distributed in human milk, although its concentration is 20% lower than in plasma. For these reasons, Zapain should be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if Zapain causes dizziness or sedation. Codeine may cause visual disturbances.

4.8 Undesirable effects

Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.

The most commonly (>1/100, <1/10) reported reactions are:

Central nervous system:	Dizziness Light-headedness Sedation Headache
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Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

4.9 Overdose

Codeine

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Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and the institution of controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Opioid antagonists may be employed. Gastric lavage should be considered. Patients should remain under observation, as per hospital guidelines and on a case per case basis.

Paracetamol

Because of its ready availability, paracetamol is often taken in overdosage. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested. The major complication is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (plasma aminotransferase > 1000 mg/l). About 1% develop fulminant hepatic failure which is usually fatal. Renal failure from acute tubular necrosis is a further uncommon complication which may develop in the absence of hepatic failure. There are no specific early manifestations of severe paracetamol poisoning. Consciousness is not impaired except in the occasional unusually severely poisoned patient with metabolic acidosis, and maximum abnormality of liver function tests is delayed for at least 3 days.

Emergency estimation of the plasma paracetamol concentration is therefore necessary to determine the severity of intoxication and the need for specific therapy with N-acetylcysteine (NAC).

Patients who have ingested more than 150 mg/kg should have gastric lavage performed if they present within an hour of ingestion. Activated charcoal may also be given. A plasma paracetamol level will indicate the likelihood of a patient developing high ALT/AST activities (i.e. > 1,000 i.u. /L) and must be measured at least 4 hours after ingestion. Plasma levels measured less than 4 hours post-ingestion cannot be interpreted. Patients with a plasma level above the treatment line require N-acetylcysteine (NAC). A paracetamol normogram should be employed to determine treatment levels.

Patients who present to an Accident and Emergency Department more than 8 hours after ingesting a paracetamol overdose are at greater risk of developing hepatic damage. In cases of severe poisoning, hepatic failure may progress to encephalopathy, coma and death.

Blood should be taken for a plasma level, but the NAC infusion should be started as soon as possible if more than 150 mg/kg was taken. The NAC infusion should not be delayed while awaiting the result of the plasma paracetamol level. Administration of the antidote should be stopped if the plasma level is subsequently found to be below the treatment line. General supportive measures must be available. At the end of the NAC infusion, blood should be taken to check the INR and creatinine concentration. If the investigations are abnormal, a further infusion of NAC (at 16 hour dose), to be continued until recovery or death, should be considered.

In the range of concentrations associated with overdosage, paracetamol may give a false positive result for plasma salicylate in tests based on the direct colour reaction with ferric ions. In the same circumstances it may induce spuriously high results for blood dextrose estimated with the YSI and Yellow Springs Model 23AM dextrose analyzers. Conversely, it may cause falsely low results for dextrose when the dextrose peroxidase/dextrose-6-phosphate dehydrogenase method is used

Liver damage following overdosage is relatively uncommon in young children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. Paracetamol is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily. The inhibitory effect of paracetamol on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function. Animal studies have indicated that paracetamol strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions).

Codeine is a centrally acting analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has an exceptionally low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. However, its antitussive actions may involve distinct receptors that bind codeine itself.

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic for about 10% of the Caucasian population.

The fixed combination of paracetamol and codeine has been shown to be effective in acute nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 min and 2 h after ingestion. Paracetamol is distributed throughout most body tissues, with an apparent volume of distribution of approximately 1 L/kg of body weight. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta. Paracetamol is extensively metabolised in the liver and the total body clearance is about 5 ml/min/1/kg. Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine.

Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 h and the plasma half-life is about 3.5 h. The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine crosses the placenta and is present in the milk of lactating mothers.

Codeine is metabolised in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), and other metabolites. After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h.

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

5.3 Preclinical safety data

There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Sodium Docusate
Sorbitol
Saccharin Sodium
Dimeticone
Sodium Benzoate
Macrogol 6000
Spray-dried natural grapefruit flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

1 year (for foil strips)

3 years (for polypropylene tube)

6.4 Special precautions for storage

Do not store above 25°C

Also for the tube pack: The polypropylene tubes must be kept tightly closed in order to protect from moisture.

6.5 Nature and contents of container

1) Strips of Aluminium / polyethylene foils

Pack size: 100 tablets.

2) Polypropylene tube with Polyethylene stopper containing a desiccant cartridge

Each tube contains 16 tablets and 6 tubes are packed in cardboard containers to give a pack size of 96 tablets.

6.6 Special precautions for disposal and other handling

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd

NLA Tower 12-16 Addiscombe Road

Croydon CR0 0XT

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0412

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/08/2010

10 DATE OF REVISION OF THE TEXT

16/08/2010

Module 3

Product Information Leaflet



PACKAGE LEAFLET: INFORMATION FOR THE USER

050248

Codipar 15mg/500mg Effervescent Tablets (Codeine Phosphate Hemihydrate 15mg and Paracetamol 500mg)

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor or pharmacist. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours. If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Codipar Effervescent Tablets are and what they are used for
2. Before you take Codipar Effervescent Tablets
3. How to take Codipar Effervescent Tablets
4. Possible side effects
5. How to store Codipar Effervescent Tablets
6. Further information

1. WHAT CODIPAR EFFERVESCENT TABLETS ARE AND WHAT THEY ARE USED FOR

Codipar Effervescent Tablets contain paracetamol and codeine. Paracetamol is an analgesic (relieves pain) and an antipyretic (lowers raised temperatures). Codeine is a painkiller. Codipar Effervescent Tablets are used for the relief of mild to severe short term pain.

2. BEFORE YOU TAKE CODIPAR EFFERVESCENT TABLETS

Codipar Effervescent Tablets should not be taken longer than as directed by your doctor. Taking codeine (an active ingredient of Codipar Effervescent Tablets) regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets. If a pain killer is used too long for headaches, it can make them worse.

Do not take Codipar Effervescent Tablets if:

- you know that you are allergic to paracetamol or codeine, or any of the other ingredients (refer to section 6 below)
- you suffer from breathing problems, for example chronic bronchitis or emphysema or are suffering an asthma attack
- you are taking monoamine oxidase inhibitors (MAOIs) or have been taking them within the last two weeks. MAOIs, such as phenelzine, moclobemide or isocarboxazid, are medicines used to treat depression
- you have just had a head injury or suffer from increased pressure on the brain
- you have severe problems with your kidneys or liver
- you drink a lot of alcohol
- you have recently had an operation to your gall bladder

Codipar Effervescent Tablets should not be taken by children under 18 years of age.

Take special care and tell your doctor or pharmacist before taking Codipar Effervescent Tablets if:

- you have any stomach pains or other sudden problems in your abdomen (belly)
- you are prone to suffer from asthma
- you are elderly
- you have liver or kidney problems, because the dose might need to be lower
- your prostate is larger than normal or you have a narrowing of your urethra (tube through which urine is passed)
- you feel you have taken Codipar Effervescent Tablets for a long time. You may develop a dependence on Codipar Effervescent Tablets which may be harmful.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines interact with each other and this can alter their effect. It is particularly important to tell your doctor or pharmacist if you are taking the following medicines:

- Medicines to treat depression such as amitriptyline, fluoxetine, sertraline etc.
- Medicines used to treat high blood pressure such as furosemide, amiloride or bendroflumethiazide
- MAOIs used to treat depression, taken within the last 14 days (refer to "do not take if" in section 2 above)
- Medicines to treat mental illness, e.g. chlorpromazine, haloperidol etc.
- Sedatives and sleeping tablets, e.g. temazepam and diazepam
- Medicines for irregular heart beats (mexiletine, quinine or quinidine)
- Drugs used to dry fluids in the mouth and lungs known as anticholinergics
- Medicines to treat diarrhoea or sickness (metoclopramide, domperidone)
- Medicines to treat epilepsy (e.g. phenytoin and carbamazepine)
- Colestyramine, used to treat high levels of lipids in your blood, or for problems related to your bile duct.
- Ritonavir, used to treat HIV
- Other strong painkillers called opioids
- Medicines which prevent blood clotting (anticoagulants such as warfarin).

Codipar Effervescent Tablets must not be taken with any other medicines containing paracetamol or codeine. Some products which can be bought without a prescription may contain paracetamol or codeine, so always check the labels for ingredients.

Taking Codipar Effervescent Tablets with food and drink
Do not drink alcohol whilst taking Codipar Effervescent Tablets.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to become pregnant speak to your doctor or pharmacist before taking this medicine.

Codipar Effervescent Tablets should not be used during pregnancy as they can affect the baby and can cause breathing problems when the baby is born.

Codipar Effervescent Tablets should not be used in breast feeding, as the active ingredients codeine phosphate hemihydrate and paracetamol can pass into the breast milk and cause harm to your baby. The following signs or symptoms can be seen in babies who have been breast fed whilst their mothers have been on this medicine, increased drowsiness, small pupils, floppy limbs and difficulty in breathing. If you are breast feeding and have been taking this medication and notice any of the symptoms mentioned in your baby **stop taking** these tablets and speak to your doctor **immediately**.

Driving and using machines

Codipar Effervescent Tablets may cause dizziness or drowsiness and you should not drive or operate machinery if you are affected this way. Codeine may disturb your vision.

Important information about some of the ingredients of Codipar Effervescent Tablets

This medicine contains sorbitol (389mg per tablet), which is a sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains 379 mg sodium in each tablet. This should be taken into consideration by patients on a controlled sodium (salt) diet.

3. HOW TO TAKE CODIPAR EFFERVESCENT TABLETS

Always take Codipar Effervescent Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking the tablets:

The tablets must be put in a glass of water and allowed to completely dissolve. Drink the resulting solution immediately. Do not chew or bite your tablets.

Dose:

The usual dosage is two tablets every four hours as needed. You should not take more than 8 tablets in 24 hours. If you feel the effect of Codipar Effervescent Tablets is too strong or too weak, speak to your doctor or pharmacist. A lower dosage may be needed if you are elderly or have other medical problems.

Check with your doctor about this. Codipar Effervescent Tablets are not recommended for children under 18 years.

If you take more Codipar Effervescent Tablets than you should Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage. Bring the remaining tablets and this leaflet with you so that the medical staff know what you have taken.

If you forget to take Codipar Effervescent Tablets

Do not take more than one dose at a time. If you forget to take a dose then take your next dose at the usual time. Never take two doses at the same time.

If you stop taking Codipar Effervescent Tablets

Codipar Effervescent Tablets can become habit forming. This is called dependence (addiction). If you stop taking your medicine suddenly it can cause withdrawal symptoms such as restlessness and irritability. Your doctor will stop your tablets gradually to avoid you having these withdrawal symptoms. If you find you need to use this product all the time, it is important to consult your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Codipar Effervescent Tablets can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body) should be reported to a doctor immediately. The following side effects are serious. Talk to your doctor straight away if you notice them:

Rarely (affecting less than 1 in 1000 people):

- Unusual bruising, or infections such as sore throats - this may be a sign of rare changes in the blood

Commonly (affecting less than 1 in 10 people):

- feeling overly elated or depressed
- shortness of breath

Also:

- difficulty in passing urine
- small eye pupils, problems with vision
- slow or weak breathing
- yellowing of the skin or whites of the eyes (symptoms of liver damage)

Other side effects include:

Commonly (affecting less than 1 in 10 people):

- feeling sick (nausea) and being sick (vomiting)
- constipation
- headache
- light headedness, dizziness, sleepiness
- stomach pains
- skin rashes or itching

If any of the side effects become serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CODIPAR EFFERVESCENT TABLETS

- Keep out of the reach and sight of children.
- Do not use Codipar Effervescent Tablets after the expiry date which is stated on the carton and the blister.
- Do not store above 25°C.

Medicines should not be disposed of via wastewater. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Codipar Effervescent Tablets contain

- The active substances are Codeine Phosphate Hemihydrate, 15mg and Paracetamol, 500mg.
- The other ingredients are sodium hydrogen carbonate, sodium carbonate anhydrous, citric acid anhydrous, sorbitol neosorb P60 W, PovidoneK30, sodium saccharin, macrogol 6000 and grapefruit flavour.

What Codipar Effervescent Tablets look like and contents of the pack

Codipar Effervescent tablets are white circular tablets, Codipar Effervescent tablets are available in aluminium:polyethylene foils strips packs of 100 effervescent tablets(25 strips of 4 tablets)

Marketing Authorisation Holder:

Goldshield Pharmaceuticals Ltd, NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CRO OXT, UK

Manufactured By:

Unither Industries, ZI du Malcourlet, 03800 Gannat, France
Date of leaflet revision: August 2010 10978/LF/A



PACKAGE LEAFLET: INFORMATION FOR THE USER
Zapain 30mg/500mg Effervescent Tablets
(Codeine Phosphate Hemihydrate 30mg and Paracetamol 500mg)

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others.
It may harm them, even if their symptoms are the same as yours.
If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Zapain Effervescent Tablets are and what they are used for
2. Before you take Zapain Effervescent Tablets
3. How to take Zapain Effervescent Tablets
4. Possible side effects
5. How to store Zapain Effervescent Tablets
6. Further information

1. What Zapain Effervescent Tablets Are And What They Are Used For

Zapain Effervescent Tablets contain paracetamol and codeine. Paracetamol is an analgesic (relieves pain) and an antipyretic (lowers raised temperatures). Codeine is a painkiller. Zapain Effervescent Tablets are used for the relief of mild to severe short term pain.

2. Before You Take Zapain Effervescent Tablets

Zapain Effervescent Tablets should not be taken longer than as directed by your doctor. Taking codeine (an active ingredient of Zapain Effervescent Tablets) regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.

If a pain killer is used too long for headaches, it can make them worse.

Do not take Zapain Effervescent Tablets if:

- you know that you are allergic to paracetamol or codeine, or any of the other ingredients (refer to section 6 below)
- you suffer from breathing problems, for example chronic bronchitis or emphysema or are suffering an asthma attack
- you are taking monoamine oxidase inhibitors (MAOIs) or have been taking them within the last two weeks. MAOIs, such as phenelzine, moclobemide or isocarboxazid, are medicines used to treat depression
- you have just had a head injury or suffer from increased pressure on the brain
- you have severe problems with your kidneys or liver
- you drink a lot of alcohol
- you have recently had an operation to your gall bladder

Zapain Effervescent Tablets should not be taken by children under 18 years of age.

Take special care and tell your doctor or pharmacist before taking Zapain Effervescent Tablets if:

- you have any stomach pains or other sudden problems in your abdomen (belly)
- you are prone to suffer from asthma
- you are elderly
- you have liver or kidney problems, because the dose might need to be lower
- your prostate is larger than normal or you have a narrowing of your urethra (tube through which urine is passed)
- you feel you have taken Zapain Effervescent Tablets for a long time. You may develop a dependence on Zapain Effervescent Tablets which may be harmful.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines interact with each other and this can alter their effect. It is particularly important to tell your doctor or pharmacist if you are taking the following medicines:

- Medicines to treat depression such as amitriptyline, fluoxetine, sertraline etc.
- Medicines used to treat high blood pressure such as furosemide, amiloride or bendroflumethiazide
- MAOIs used to treat depression, taken within the last 14 days (refer to “do not take if” in section 2 above)
- Medicines to treat mental illness, e.g. chlorpromazine, haloperidol etc
- Sedatives and sleeping tablets, eg temazepam and diazepam
- Medicines for irregular heart beats (mexiletine, quinine or quinidine)
- Drugs used to dry fluids in the mouth and lungs known as anticholinergics
- Medicines to treat diarrhoea or sickness (metoclopramide, domperidone)
- Medicines to treat epilepsy (e.g. phenytoin and carbamazepine)
- Colestyramine, used to treat high levels of lipids in your blood, or for problems related to your bile duct.
- Ritonavir, used to treat HIV
- Other strong painkillers called opioids
- Medicines which prevent blood clotting (anticoagulants such as warfarin).

Zapain Effervescent Tablets must not be taken with any other medicines containing paracetamol or codeine. Some products which can be bought without a prescription may contain paracetamol or codeine, so always check the labels for ingredients.

Taking Zapain Effervescent Tablets with food and drink

Do not drink alcohol whilst taking Zapain Effervescent Tablets.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to become pregnant speak to your doctor or pharmacist before taking this medicine. Zapain Effervescent Tablets should not be used during pregnancy as they can affect the baby and can cause breathing problems when the baby is born. Zapain Effervescent Tablets should not be used in breast feeding, as the active ingredients codeine phosphate hemihydrate and paracetamol can pass into the breast milk and cause harm to your baby. The following signs or symptoms can be seen in babies who have been breast fed whilst their mothers have been on this medicine, increased drowsiness, small pupils, floppy limbs and difficulty in breathing. If you are breast feeding and have been taking this medication and notice any of the symptoms mentioned in your baby **stop taking** these tablets and speak to your doctor **immediately**.

Driving and using machines

Zapain Effervescent Tablets may cause dizziness or drowsiness and you should not drive or operate machinery if you are affected this way. Codeine may disturb your vision.

Important information about some of the ingredients of Zapain Effervescent Tablets

This medicine contains sorbitol (487mg per tablet), which is a sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains 413 mg sodium in each tablet. This should be taken into consideration by patients on a controlled sodium (salt) diet.

3. How To Take Zapain Effervescent Tablets

Always take Zapain Effervescent Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking the tablets:

The tablets must be put in a glass of water and allowed to completely dissolve. Drink the resulting solution immediately. Do not chew or bite your tablets.

Dose:

The usual dosage is one or two tablets every four hours as needed. You should not take more than 8 tablets in 24 hours. If you feel the effect of Zapain Effervescent Tablets is too strong or too weak, speak to your doctor or pharmacist.

A lower dosage may be needed if you are elderly or have other medical problems.

Check with your doctor about this.

Zapain Effervescent Tablets are not recommended for children under 18 years.

If you take more Zapain Effervescent Tablets than you should

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage. Bring the remaining tablets and this leaflet with you so that the medical staff know what you have taken.

If you forget to take Zapain Effervescent Tablets

Do not take more than one dose at a time. If you forget to take a dose then take your next dose at the usual time. Never take two doses at the same time.

If you stop taking Zapain Effervescent Tablets

Zapain Effervescent Tablets can become habit forming. This is called dependence (addiction). If you stop taking your medicine suddenly it can cause withdrawal symptoms such as restlessness and irritability. Your doctor will stop your tablets gradually to avoid you having these withdrawal symptoms. If you find you need to use this product all the time, it is important to consult your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zapain Effervescent Tablets can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body) should be reported to a doctor immediately.

The following side effects are serious. Talk to your doctor straight away if you notice them:

Rarely (affecting less than 1 in 1000 people):

- Unusual bruising, or infections such as sore throats - this may be a sign of rare changes in the blood

Commonly (affecting less than 1 in 10 people):

- shortness of breath
- feeling overly elated or depressed

Also:

- difficulty in passing urine
- small eye pupils, problems with vision
- slow or weak breathing
- yellowing of the skin or whites of the eyes (symptoms of liver damage)

Other side effects include:

Commonly (affecting less than 1 in 10 people):

- feeling sick (nausea) and being sick (vomiting)
- constipation
- headache
- light headedness, dizziness, sleepiness
- stomach pains
- skin rashes or itching

If any of the side effects become serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

5. How To Store Zapain Effervescent Tablets

- Keep out of the reach and sight of children.
- Do not use Zapain Effervescent Tablets after the expiry date which is stated on the carton and the blister.
- Do not store above 25°C. Keep the tubes tightly closed in order to protect from moisture.

Medicines should not be disposed of via wastewater. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Zapain Effervescent Tablets contain

- The active substances are Codeine Phosphate Hemihydrate, 30mg and Paracetamol, 500mg.
- The other ingredients are sodium hydrogen carbonate, sodium carbonate anhydrous, citric acid anhydrous, sodium docusate, sorbitol, saccharin sodium, dimeticone, sodium benzoate, macrogol 6000 and spray-dried natural grapefruit flavour.

What Zapain Effervescent Tablets look like and contents of the pack

Zapain Effervescent tablets are white circular tablets with a score line on one face, although your tablets are scored they must not be halved as they will not give an equal dose.

Zapain Effervescent tablets are available in aluminium: polyethylene foils strips packs of 100 effervescent tablets (25 strips of 4 tablets) or in polypropylene tubes.

Each tube contains 16 tablets and 6 tubes are packed in cardboard containers to give a pack size of 96 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Goldshield Pharmaceuticals Ltd,

NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CRO OXT, UK

Manufactured By:

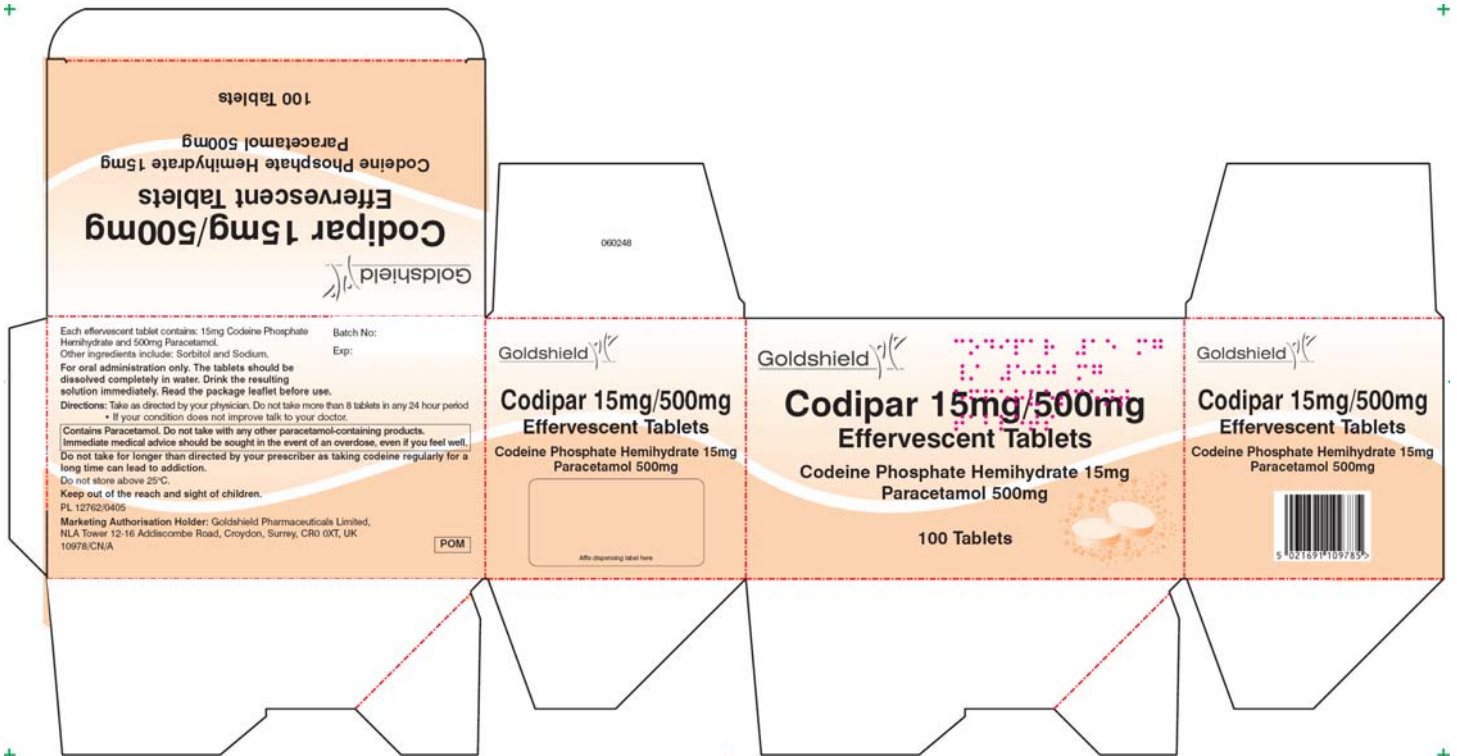
Unither Industries,

ZI du Malcourlet, 03800 Gannat, France

Date of leaflet revision: August 2010


101798/LF/A

Module 4 Labelling



<p style="text-align: center;">Goldshield </p> <p style="text-align: center;">Codipar 15mg/500mg Effervescent Tablets</p> <p style="text-align: center;">Codeine Phosphate Hemihydrate 15mg Paracetamol 500mg</p> <p style="text-align: center;">MA Holder: Goldshield Pharmaceuticals Ltd. PL No: 12762/0405 10978/FL/A</p>	<p style="text-align: center;">Goldshield </p> <p style="text-align: center;">Codipar 15mg/500mg Effervescent Tablets</p> <p style="text-align: center;">Codeine Phosphate Hemihydrate 15mg Paracetamol 500mg</p> <p style="text-align: center;">MA Holder: Goldshield Pharmaceuticals Ltd. PL No: 12762/0405 10978/FL/A</p>
<p style="text-align: center;">Goldshield </p> <p style="text-align: center;">Codipar 15mg/500mg Effervescent Tablets</p> <p style="text-align: center;">Codeine Phosphate Hemihydrate 15mg Paracetamol 500mg</p> <p style="text-align: center;">MA Holder: Goldshield Pharmaceuticals Ltd. PL No: 12762/0405 10978/FL/A</p>	<p style="text-align: center;">Goldshield </p> <p style="text-align: center;">Codipar 15mg/500mg Effervescent Tablets</p> <p style="text-align: center;">Codeine Phosphate Hemihydrate 15mg Paracetamol 500mg</p> <p style="text-align: center;">MA Holder: Goldshield Pharmaceuticals Ltd. PL No: 12762/0405 10978/FL/A</p>



Pharma Code: 360	Goldshield 
Bar Code: 5021691017981	
Origination by: David Nader	A/Work sign Off:
Revision by: David Nader	Final signatures:
Revision date: 05/08/2010	Date:
Cols: PMS 668C & Black	
Account Handler: Simon	



Goldshield 

Zapain 30mg/500mg Effervescent Tablets

Codeine Phosphate Hemihydrate 30mg
Paracetamol 500mg

16 Tablets

040247

Each effervescent tablet contains: Codeine Phosphate Hemihydrate 30mg and Paracetamol 500mg.
Other ingredients include: Sorbitol and Sodium. Please read the package leaflet before use.

For oral administration only.

Directions: Take as directed by your physician. Do not take more than 8 tablets in any 24 hour period
• If your condition does not improve talk to your doctor.

**Contains Paracetamol. Do not take with any other paracetamol-containing products.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.**

Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

Do not store above 25°C. Keep the tubes tightly closed in order to protect from moisture.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Marketing Authorisation Holder: Goldshield Pharmaceuticals Limited, PL 12762/0412
NLA Tower 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, UK 101798/TU/A **POM**

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the applications for Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets could be approved. These products are prescription only medicines (POM) indicated for the relief of mild to severe acute pain.

These applications for Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets are submitted as abridged applications according to Article 10.a of Directive 2001/83/EC, claiming to be 'well established use' applications.

Paracetamol, a para-aminophenol derivative, is only a weak inhibitor of prostaglandin synthesis, but it is known to inhibit substance P-induced hyperalgesia and also reduces nitric oxide generation in response to NMDA receptor activation and substance P. Paracetamol is readily absorbed from the gastrointestinal tract, and distributed into most tissues, with negligible plasma protein binding at normal doses. Metabolism occurs predominantly in the liver, with 90-100% of the drug recoverable in urine as conjugates after 24 hours. Cytochrome P450-mediated N-hydroxylation of a small amount of the drug results in the production of N-acetyl-p-amino-benzoquinoneimine (NAPQI), which is neutralised by combining with sulphhydryl groups in hepatic glutathione. Following ingestion of large amounts of paracetamol, hepatic glutathione is depleted, and the NAPQI reacts instead with sulphhydryl groups on hepatic proteins. This can lead to subacute hepatic necrosis and in severe cases to hepatic failure.

Codeine, a phenanthrene derivative, is much less potent as an analgesic than morphine and has relatively mild sedative properties. Codeine is a pure agonist and is particularly selective for μ receptors. Overall however, codeine has a low affinity for opioid receptors and its analgesic effect is due to its conversion to morphine. Codeine is absorbed from the gastrointestinal tract and metabolised by O- and N-demethylation in the liver to morphine, norcodeine and other metabolites. The conversion of codeine to morphine is effected by CYP2D6, an isoenzyme that may be deficient in about 10% of the population, termed poor metabolisers. Other CYP2D6 polymorphisms can lead to enhanced metabolism, termed ultra-rapid metabolisers. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Regular administration of codeine, like any opioid analgesic, can lead to dependence, which is satisfied by μ receptor agonists.

No new preclinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances. No clinical studies with the exception of the bioequivalence study have been performed and none are required for this application as the pharmacology of paracetamol and codeine phosphate hemihydrate is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those

countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets
Name(s) of the active substance(s) (INN)	Paracetamol and Codeine Phosphate
Pharmacotherapeutic classification (ATC code)	Anilides, paracetamol combinations (N02B E51)
Pharmaceutical form and strength(s)	15mg/500mg and 30mg/500mg effervescent tablets
Reference numbers for the Decentralised Procedure	UK/H/1866 and 3322/001/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 12762/0405 and 0412
Name and address of the authorisation holder	Goldsheild Pharmaceuticals Limited NLA Tower 12-16 Addiscombe Road Croydon CR0 0XT UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

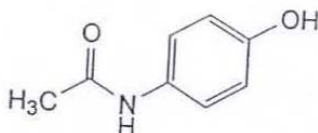
III.1 QUALITY ASPECTS

S. Active substance

Paracetamol

INN/Ph.Eur name: Paracetamol
Chemical name: Acetaminophen
or N-Acetyl-p-aminophenol
or N-(4hydroxyphenyl)acetamide

Structural formula:



Molecular formula: $C_8H_9NO_2$

Appearance: white, free-flowing easily blendable powder.

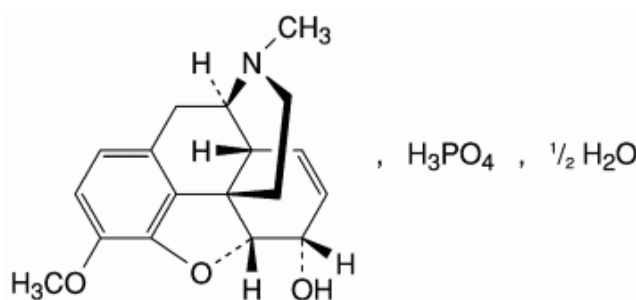
Molecular weight: 151.2

Paracetamol complies with its European Pharmacopoeia monograph.

Codeine Phosphate Hemihydrate

INN/Ph.Eur name: Codeine phosphate hemihydrate/Codeine phosphate
Chemical name: 7, 8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol
phosphate hemihydrate.

Structural formula:



Molecular formula: $C_{18}H_{24}NO_7P, \frac{1}{2}H_2O$

Appearance: White or almost white, crystalline powder or small colourless crystals.

Solubility: Freely soluble in water, slightly soluble or very slightly soluble in ethanol (96%).

Molecular weight: 406.4

Codeine Phosphate Hemihydrate complies with its European Pharmacopoeia monograph.

All aspects of the manufacture of the active substances paracetamol and codeine phosphate hemihydrate from their starting materials are controlled by a Certificate of Suitability.

Synthesis of the drug substances from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients.

An appropriate specification is provided for the active substances, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substances to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

The tablets consists of pharmaceutical excipients sodium hydrogen carbonate, sodium carbonate anhydrous, citric acid anhydrous, sorbitol neosorb P60 W, povidone K30, sodium saccharin, sacrogol 6000 and grapefruit flavour.

With the exception of grapefruit flavour, all excipients comply with their respective European Pharmacopoeia monographs. Grapefruit flavour complies with suitable in-house specifications.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Satisfactory impurity profiles have been provided.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on commercial-scale batches for Zapain 30mg/500mg Effervescent Tablets have been provided. Satisfactory validation data on pilot-scale batches for Codipar 15mg/500mg Effervescent Tablets have been provided. The applicant has committed to perform process validation on the first three commercial-scale batches of Codipar 15mg/500mg Effervescent Tablets produced post approval.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets are packaged in:

1) Blister strips composed of polyethylene (PE) and aluminium. Each strip contains 4 tablets individually wrapped in cardboard containers to give a pack size of 100 tablets.

Zapain 30mg/500mg Effervescent Tablets are also packaged in:

2) Polypropylene tube with Polyethylene stopper containing a desiccant cartridge
Each tube contains 16 tablets and 6 tubes are packed in cardboard containers to give a pack size of 96 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product

Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of:

For Codipar 15mg/500mg Effervescent Tablets: 18 months with the special storage instructions, 'Do not store above 25°C'.

For Zapain 30mg/500mg Effervescent Tablets: 1 year (for the blister strips) and 3 years (for the polypropylene tube). Special storage instructions are: 'Do not store above 25°C', and additionally for the polypropylene tube: 'must be kept tightly closed in order to protect from moisture'.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPCs, PIL and labelling are pharmaceutically acceptable. Please find the UK PIL and label mock-ups in modules 3 and 4.

User testing results have been submitted for the PIL for these products. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRE-CLINICAL ASSESSMENT

The pharmacodynamics, pharmacokinetics and toxicological properties of paracetamol and codeine phosphate hemihydrate are well-known. As paracetamol and codeine phosphate hemihydrate are widely used, well-known active substances, the applicant has not provided any new pre-clinical data and none are required for these 'well established use' applications.

The impurities associated with the drug substance and drug product appear to be well controlled and within the limits set out in ICH guidelines and in the European Pharmacopeia, therefore it is unlikely that any toxicological qualification is necessary.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A satisfactory justification has been provided for non-submission of an environmental risk assessment.

It is recommended that a Marketing Authorisation is granted for these applications.

CLINICAL ASSESSMENT

No new pharmacokinetic, pharmacodynamic, efficacy or safety data were submitted with these applications and none were required as these are ‘well established use’ applications and the active substances paracetamol and codeine phosphate hemihydrate, are well-known, widely used substance. As these are bibliographic applications, a literature review of published literature was submitted.

1. CLINICAL PHARMACOLOGY

1.1 Pharmacokinetics

1.1.1 Absorption

Paracetamol

Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 minutes and 2 hours after ingestion, depending on the formulation.

Paracetamol absorption is negligible from the stomach but very rapid from the small intestine and the rate of absorption therefore depends on the rate of gastric emptying. Oral bioavailability is about 80% and is independent of dose in the range 5-20 mg/kg. The usual therapeutic doses produce plasma concentrations of 5 to 20 µg/ml.

Codeine

Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 hour. The oral intramuscular analgesic potency ratio is 1:1.5, which demonstrates that the oral bioavailability of codeine is greater than that of morphine.

Table 1 below from a cross-over study design in four healthy male subjects, depicts the pharmacokinetic parameters after 15, 30 and 60 mg codeine administered orally:

Table 1: PK of codeine 15, 30, 60 mg¹

	Subject	15 mg			30 mg			60 mg		
		C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC* (ng ml ⁻¹ h)
Codeine	1	36	0.5	108	74	0.5	242	128	1.0	405
	2	28	0.5	104	71	0.5	229	111	1.0	435
	3	38	1.0	128	55	1.0	204	117	1.0	492
	4	27	0.5	85	43	1.0	190	100	1.5	423
	Mean	32	0.6	106	61	0.8	216	114	1.1	439
	s.d.	6	0.3	18	15	0.3	24	12	0.3	38

In this study, codeine kinetics were adequately described by a one-compartment open model with first-order absorption

¹ Findlay JW, et al., 1986.

Combination

Eight healthy male volunteers took part in a study to determine the relative bioavailability of 500 mg paracetamol tablets, 500 mg paracetamol plus 30 mg codeine phosphate tablets and 750 mg paracetamol suppositories against commercial tablets (500 mg paracetamol). Plasma levels of paracetamol and codeine were determined by HPLC and the pharmacokinetic parameters established. The AUC data for paracetamol showed that all four preparations were bioequivalent.

The pharmacokinetic data of codeine from the fixed combination tablet were compared with corresponding data from the literature. The bioequivalence of codeine when based on this comparison can also be assured, showing that there is no reciprocal influence of codeine and paracetamol on the absorption of the other ingredient of the fixed combination².

In another study, the plasma concentrations of paracetamol and codeine were determined in a cross-over study in twelve healthy volunteers after oral and rectal application of a compound preparation. Values of C_{max} for codeine and paracetamol were 124 ng/ml and 16.5 µg/ml, respectively. These values are comparable to those previously reported after the oral administration of equal doses (60 mg and 1000 mg, respectively) of the single compounds.

The influence of codeine on paracetamol absorption was indirectly investigated by administering iv codeine (1 mg/kg) and saline on in 10 healthy human volunteers using a double-blind, randomized, cross-over design. Gastric emptying was studied using the paracetamol absorption test. Results showed that C_{max} of paracetamol was not significantly altered by codeine³. These results are explained by the fact that paracetamol is mostly absorbed by the small intestine but provide a further demonstration of the lack of interaction with codeine. Furthermore, serum paracetamol concentrations in acute overdosage are not altered by the co-ingestion of opioids⁴.

Plasma and urine concentrations of codeine and its measurable metabolites were determined by HPLC in six healthy subjects after a single 30 mg oral dose of codeine either alone or after 7 doses of 1 g paracetamol 8 hourly. After codeine alone, the t_{1/2} (h), AUC (µmol/l x h) and CLR (ml/min) for codeine were 2.2, 0.81, and 252 respectively. These were not significantly altered by paracetamol: 2.2, 0.84, and 291 respectively. For codeine-6-glucuronide the values were 2.4, 22.0, and 29.7 respectively. These were not significantly different from those after codeine plus paracetamol: 2.4, 21.9, and 39.611.

1.1.2 Distribution

Codeine

The volume of distribution is approximately 3.6 l/kg. Codeine enters the tissues rapidly and is concentrated in the kidney, lung, liver and spleen. The bulk of the total drug is in the skeletal muscle. The brain does not accumulate high levels of the opiate. Within the brain, 80% or more is associated with opiate receptors, which are especially concentrated in the caudate nucleus, amygdala, and periaqueductal grey matter of the hypothalamus, midbrain and medial thalamus. Codeine crosses the placenta and is present in the milk of lactating mothers. The relationship between plasma levels of codeine and its therapeutic effect has not been studied extensively.

² Klein G, et al., 1986.

³ Crighton IM, et al., 1998.

⁴ Waring WS, et al., 2008.

Paracetamol

Paracetamol is distributed throughout most body tissues, with an apparent volume of distribution of approximately 1 L/kg of body weight. A clinically insignificant proportion of the drug binds to plasma proteins. The concentrations of paracetamol in saliva are similar to those in plasma. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta.

1.1.3 Metabolism and Elimination

Paracetamol

Paracetamol is extensively metabolized in the liver and the total body clearance is about 5 ml/min/1/kg. Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine. Its renal clearance is about 10 ml/min and is weakly dependent on urine flow rate but not on pH^{5,6}. *In vitro* and animal data indicate that small quantities of paracetamol are metabolized by a cytochrome P-450 microsomal enzyme to a reactive intermediate metabolite (Nacetyl- *p*-benzoquinoneimine, *N*-acetylimidoquinone, NAPQI) which is further metabolized via conjugation with glutathione and ultimately excreted in urine as a mercapturic acid. It has been suggested that this intermediate metabolite is responsible for paracetamol-induced liver necrosis and that high doses of paracetamol may deplete glutathione so that inactivation of this toxic metabolite is decreased. At high doses, the capacity of metabolic pathways for conjugation with glucuronic acid and sulphuric acid may be exceeded, resulting in increased metabolism of paracetamol by alternative pathways. Drugs that potentially modify these metabolic processes are used (e.g., acetylcysteine) or are being studied (e.g., cysteine, mercaptamine) as antidotes for paracetamol-induced hepatotoxicity[6].

The mean plasma paracetamol half-life after a therapeutic dose is about 2.3 hours in healthy adults with a range of 1.5-3.0 hours.

Codeine

Plasma half-life is about 3.5 hours.

Total body clearance of codeine is approximately 0.85 l/min.

After an oral dose, about 86% is excreted in the urine in 24 hours as free drug and metabolites, mostly in the form of metabolites. Some drug is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h, which may be increased to about 10% when the urinary pH is decreased⁶.

The renal clearance of codeine was 183 ± 59 ml/min in healthy volunteers after the oral administration of 30 mg codeine and was inversely correlated with urine pH ($r = 0.81$). These data suggest that codeine undergoes filtration at the glomerulus, tubular secretion and passive reabsorption. The renal clearance of codeine-6-glucuronide (one of its major metabolites; see below) was 55 ± 21 ml/min, and was not correlated with urine pH. Its binding to human plasma was less than 10%. These data suggest that codeine-6-glucuronide undergoes filtration at the glomerulus and tubular reabsorption. This latter process is unlikely to be passive⁷.

⁵ AHSF Monograph, 2008.

⁶ Therapeutic Drugs, 1999.

⁷ Chen ZR, et al., 1991.

Codeine is metabolized in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), *N*-demethylation to form *nor*codeine, and conjugation to form glucuronides and sulphates of both codeine and its metabolites. Of the excreted material in urine, 40-70% is free or conjugated codeine, 5-15% is free or conjugated morphine, 10-20% is free or conjugated *nor*codeine, and very small amounts may be free or conjugated *norm*morphine together with other trace metabolites. The analgesic effect of codeine is the result of its conversion to morphine by the genetically polymorphic CYP2D6 which is absent in 7-10% of the white population and present in the remainder. Poor metabolisers of debrisoquine may show absence of analgesia following codeine administration. To address this issue, the kinetics of codeine and seven of its metabolites codeine-6-glucuronide (C6G), *nor*codeine (NC), NCglucuronide (NCG), morphine (M), M-3 (M3G) and 6-glucuronides (M6G), and *norm*morphine (NM) were investigated after a single oral dose of 50 mg codeine phosphate in 14 healthy Caucasian subjects including eight extensive (EM) and six poor (PM) hydroxylators of debrisoquine. The plasma and urine concentrations of codeine and the metabolites were measured by HPLC. The mean area under the curve (AUC), half-life and total plasma clearance of codeine were 1020 ± 340 nmol l⁻¹ h, 2.58 ± 0.57 h and 2.02 ± 0.73 l h⁻¹ kg⁻¹, respectively. There were no significant differences between EM and PM in these aspects. PM had significantly lower AUC of M3G, the active metabolites M6G, NM and M ($P < 0.0001$), and lower partial metabolic clearance by *O*-demethylation ($P < 0.0001$). In contrast, the PM had higher AUC of NC ($P < 0.05$) than the EM. There was no difference between PM and EM in the AUC of C6G and NCG, nor in the partial clearances by *N*-demethylation and glucuronidation. Among EM, the AUC of C6G was 15 times higher than that of codeine, which in turn was 50 times higher than that of M. The AUCs of M6G and NM were about 6 and 10 times higher than that of M, respectively. The partial clearance by glucuronidation was about 8 and 12 times higher than those by *N*- and *O*-demethylations, respectively. The clinically important findings were the negligible plasma concentration of the *O*demethylated active metabolites M6G, NM and M in PM, and the relatively high concentrations of M6G and NM in EM. Considering the low plasma concentration of M as well as the potent analgesic effects of M6G and NM, the latter compounds might play an important role in the analgesic effect of codeine⁸.

Combination

Influence of codeine on paracetamol excretion and/or metabolism

The effect of codeine on the metabolism of paracetamol was studied in 24 healthy volunteers. No major effect on the metabolism of paracetamol was observed after the administration of codeine. Less free and total paracetamol was excreted after the combination with codeine (and caffeine) but the difference was not statistically significant in the cumulative 0-24 h period⁹.

In another study, carried out in nine healthy volunteers, the clearance and metabolism of paracetamol 1000 mg i.v. was evaluated with and without two concomitant oral doses of codeine in order to investigate a possible interaction. Plasma paracetamol was followed for 720 min and urine was collected for 24 h after each dose for determination of metabolites. When codeine was co-administered, the average total clearance of paracetamol and its clearance by glucuronidation, sulphation and mercapturate formation were 0.58 to 1.12-times the control values. It was concluded that therapeutic doses of codeine do not influence the clearance or metabolism of paracetamol¹⁰.

⁸ Yue QY, et al, 1991.

⁹ Thomas BH, et al., 1972

¹⁰ Sonne J, et al., 1988

However, it should be noted that codeine inhibits paracetamol glucuronidation *in vitro*, and this effect could have clinical consequences for prolonged periods of treatment with the fixed combination¹¹. Glucuronidation of paracetamol by human liver microsomes and the effects of aliphatic alcohols and opiates, including codeine, were investigated, as inhibitors of paracetamol glucuronidation. Furthermore, the effects of paracetamol on morphine-3 and codeine glucuronidation were investigated. Enzyme kinetic analysis was carried out via determination of the parameters K_m , V_{max} , K_i and the type of inhibition. Except for methanol and ethanol, all investigated alcohols inhibited glucuronidation of paracetamol. All tested opiates inhibited paracetamol glucuronidation with K_i values between 4.02 mmol/l (dihydrocodeine) and 11.44 mmol/l (morphine). Paracetamol itself turned out to be an inhibitor of opiate glucuronidation. The apparent K_i values were 4.62 mmol/l (inhibition of morphine-3 glucuronidation) and 9.44 mmol/l (inhibition of codeine glucuronidation). A mixed inhibition type was determined for all substances. The *in vitro* studies show a great inhibition potential for the analysed substances. Transferring the results to the *in vivo* situation, a higher liver toxicity of paracetamol can be assumed, if concomitantly a lot of alcoholic beverages with congener alcohols or if opiates are taken in higher doses. However, applied together in low doses (30-50 mg codeine and 1 g paracetamol), codeine had no effect on codeine metabolism and paracetamol had no effect on codeine metabolism.

Influence of paracetamol on codeine excretion and/or metabolism

In six healthy subjects after a single 30 mg oral dose of codeine either alone or after 7 doses of 1 g paracetamol 8 hourly, CLR (ml/min) for was not significantly altered by paracetamol. The urinary excretion of codeine-6-glucuronide, morphine, *norcodeine*, and codeine were not significantly different between the two treatments, indicating that also metabolism of codeine is not influenced by the co-administration of paracetamol.

1.1.4 Pharmacokinetics in target population

There are no specific studies focussed on possible alterations in the pharmacokinetic profiles of codeine and paracetamol in pain patients, despite the consideration that pain may be associated with some physiological changes such as gastric stasis. However, an examination of the oral/parenteral relative analgesic potency ratio of codeine in patients with cancer, demonstrated that this drug retains at least half of its analgesic activity when administered orally. This oral/parenteral relative potency ratio based on total analgesic effect is remarkably similar to the oral/parenteral bioavailability ratio for codeine based on areas under the codeine plasma curves in healthy volunteers¹². This suggests that no significant pharmacokinetic alteration is apparent in pain patients.

1.1.5 Special populations

The combination product is not recommended in children under the age of 18 years. For the elderly, a reduced dose may be required.

Codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure. It should thus not be used in diverticulitis and following bowel surgery, or in patients with acute colitis. Hypovolemia can be exacerbated by codeine, so the drug should be used with caution in these circumstances.

The pharmacokinetics and pharmacodynamics of codeine and its metabolites codeine glucuronide, morphine, and morphine glucuronide were assessed after the administration of a

¹¹ Boldt P, et al., 2007

¹² Beaver WT, et al., 1978.

single 60 mg oral dose of codeine sulfate and a single 60 mg intravenous dose of codeine phosphate in six healthy volunteers and six patients on chronic haemodialysis. Codeine elimination half-life and mean residence time were increased significantly in the haemodialysis group (18.69 ± 9.03 hours and 12.77 ± 7.09 hours, mean \pm SD, respectively) compared with the healthy volunteer group (4.04 ± 0.60 hours and 3.90 ± 0.52 hours, respectively). The total body clearance and volume of distribution of codeine were not significantly different between groups. Peak concentrations, times to peak concentrations, and AUCs for the three metabolites were also not significantly different between the groups, in part as a result of significant interpatient variability in the haemodialysis group. Adjustment of dosage regimen may be required in some patients with uraemia receiving multiple-dose codeine therapy¹³. The analgesic activity of codeine depends on transformation into the active metabolite morphine. If metabolism is decreased in patients with chronic liver disease, the analgesic action of codeine may be compromised. The kinetics of paracetamol elimination have been investigated in patients with renal, hepatic, thyroid, and gastrointestinal disease. No clinically significant changes were observed except in patients with severe acute and decompensated chronic liver disease in whom the half-life was considerably prolonged. In patients with chronic renal failure there was marked accumulation of paracetamol conjugates. Care should be taken in patients with liver and kidney disease with suitable dose reductions as appropriate. The product is contraindicated in severe liver disease and severe renal impairment.

1.1.7 Interactions

Dependence of codeine analgesia on morphine formation via CYP2D6 makes this effect liable to interaction with drugs that are inhibitors of CYP2D6. Examples of potent inhibitors of CYP2D6 are quinidine, some selective serotonin reuptake inhibitors and some neuroleptics. Less potent inhibitors, such as tricyclic antidepressants, will probably also reduce the pain relieving effect of codeine, since codeine has a low affinity for CYP2D6¹⁴.

Alcohol, opiates and anticonvulsants (including phenytoin, barbiturates, carbamazepine) that induce hepatic microsomal enzymes may increase paracetamol-induced liver toxicity because of increased conversion of the drug to hepatotoxic metabolites.

The oral anticoagulant warfarin is a racemic mixture of two enantiomers, (R) and (S). Many relevant drug interactions with warfarin have been attributed to the specific metabolic inhibition of the elimination of the more pharmacologically active (S)-enantiomer. There is considerable controversy regarding the possible interaction of paracetamol with warfarin in its potential to increase its anticoagulant effects because of discrepancies between observational studies and those in healthy volunteers. To investigate reports that acetaminophen can potentiate the anticoagulant effect of warfarin, 20 healthy male volunteers were each given single oral 20 mg doses of racemic warfarin on three separate occasions: (1) alone, (2) after 1 day of acetaminophen (4 g/d), and (3) after 2 weeks of acetaminophen (4 g/d). The urinary excretion pattern of acetaminophen and its metabolites was not significantly altered over its course of administration. The (R)- and (S)-enantiomers of warfarin exhibited significantly different pharmacokinetic properties. However, acetaminophen did not alter the disposition of either (R)- or (S)-warfarin. All subjects exhibited a pharmacodynamic response to racemic warfarin. The response was not significantly altered in the presence of acute or chronic acetaminophen dosing, as assessed by prothrombin time and factor VII

¹³ Guay DR, et al., 1988.

¹⁴ Armstrong SC, et al., 2003.

concentrations¹⁵. However, different results were obtained in another more recent double-blind placebo-controlled, randomized, cross-over study, 20 patients on stable oral anticoagulant therapy with warfarin for at least 1 month were randomized to receive placebo or paracetamol 1g four times daily for 14 days. International Normalized Ratio (INR) and clotting factors activities were measured before the first administration and then on days 2, 4, 7, 9, 11, 14. Mean INR rose rapidly after the start of paracetamol and was significantly increased within one week of paracetamol intake compared to placebo, $p=0.0002$. The INR values reached a mean maximum of 3.45 ± 0.78 with paracetamol versus 2.66 ± 0.73 with placebo ($p=0.03$), corresponding to a maximum increase from baseline of 1.20 ± 0.62 with paracetamol versus 0.37 ± 0.48 with placebo ($p<0.001$). Together with the rise in INR on paracetamol treatment there were significant reductions in the vitamin K-dependent clotting factors II, VII, IX and X. The most plausible hypothesis to explain the in vivo interaction is that paracetamol (or its metabolites) interfere with enzymes involved in vitamin K-dependent coagulation factor synthesis¹⁶.

Because the absorption of paracetamol is so dependent on gastric emptying, other drugs that alter gastric emptying (such as metoclopramide and domperidone) can change its pharmacokinetics; but this would not cause serious adverse effects¹⁷.

Although cholestyramine decreases the oral absorption of many concurrently administered drugs, no reports about a possible interaction with paracetamol have been found in the scientific literature.

1.2 Pharmacodynamics

1.2.1 Primary pharmacology

Paracetamol

Paracetamol has antipyretic and analgesic actions together with negligible anti-inflammatory activity by a mechanism similar to that of salicylates. Unlike salicylates, however, paracetamol does not have uricosuric activity. These effects are thought to be related to inhibition of prostaglandin synthesis. In this respect paracetamol has greater tissue selectivity than aspirin and the non-steroidal anti-inflammatory drugs. The reason for this difference is unknown.

Unlike other drugs in this therapeutic class, paracetamol does not have an anti-inflammatory effect at clinically relevant doses in humans, perhaps because it has different dose-response relations with the prostaglandins involved in fever, pain and the process of inflammation. The effects of paracetamol on cyclooxygenase activity have not been fully determined. Paracetamol is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily. The inhibitory effect of paracetamol on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function. Animal studies have indicated that paracetamol strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions). This dose-response relation is observed clinically with ASA in that a higher dose is required for anti-inflammatory effects than for analgesia or antipyresis¹⁸.

¹⁵ Kwan D, et al., 1999.

¹⁶ Mahe I, et al., 2006.

¹⁷ Toes MJ, et al., 2005.

¹⁸ Jackson CH, et al. 1984.

Codeine

The pharmacological properties of opioids result from their binding to central opioid receptors. More precisely, their analgesic action mostly depends on their binding to μ (mu) receptors, mainly in supraspinal sites, and to κ (kappa) receptors, essentially medullary. δ (delta) receptors might be also involved in these mechanisms but their role is more controversial.

Although morphine and related drugs have been used for very long years, their mechanisms of action are not still fully elucidated. However, it is well established that the analgesic effects of opioids arise from their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain *via* the rostral ventromedial medulla to the spinal cord dorsal horn. Opioid peptides and their receptors are found throughout these descending pain control circuits. Paralleling the important insights into mechanisms of opioid-induced analgesia at the brainstem and spinal levels, progress also has been made in understanding forebrain mechanisms. The actions of opioids in bulbospinal pathways are crucial into their analgesic efficacy, but the precise role of forebrain actions of opioids and whether these actions are independent of those in the bulbospinal pathways are less well defined.

Codeine exerts its effect through μ opioid receptors, although codeine has an exceptionally low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. However, its antitussive actions may involve distinct receptors that bind codeine itself¹⁹. The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to covert codeine to morphine, thus making codeine ineffective as an analgesic for about 10% of the Caucasian population.

The relief of pain by morphine-like opioids, such as codeine, is relatively selective, in that other sensory modalities are not affected. Patients frequently report that the pain is still present but that they feel more comfortable. Continuous dull pain is relieved more effectively than sharp intermittent pain, but with sufficient amount of drug it is possible to relieve even the severe pain associated with renal or biliary colic²⁰.

The primary pharmacodynamic effects of paracetamol/codeine and paracetamol were evaluated in a double-blind, placebo controlled, three-way cross over study. Healthy volunteers received paracetamol 1000 mg, paracetamol 100 mg plus codeine 60 mg and placebo in each of 3 study periods. Pain threshold and brain evoked potentials to laser stimulation were determined hourly for 6 h in 12 healthy volunteers. Pain threshold was significantly elevated compared to placebo 1 and 2 h after paracetamol ingestion. Paracetamol/codeine was superior to placebo 1 to 6 h after medication. Only at 1 and 2 h after ingestion the combined drug was better than paracetamol. The evoked potentials were significantly depressed compared to placebo 2 and 4 h after paracetamol. The combination of paracetamol and codeine was superior to placebo 1 to 6 h after ingestion. The potentials showed no difference between the two active drugs. The total analgesic effect (approximation of area under the time-efficacy curve), showed that the combined drug was superior to plain paracetamol. A higher incidence of adverse effects in 10 of the 12 subjects was observed after ingestion of the combined drug compared to plain paracetamol (1 of 12). There was at least 1 h between the peak plasma concentration of paracetamol and the peak hypoalgesia²¹.

¹⁹ Gutstein HB, et al., 2006.

²⁰ Brasseur L, 1997.

²¹ Arendt-Nielsen L, et al., 1991.

1.2.2 Secondary pharmacology

Paracetamol

Paracetamol lowers body temperature in patients with fever but rarely lowers normal body temperature. The drug acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow.

Codeine

Central actions

The mechanisms involved in euphoria, tranquillisation and changing mood are not still clearly elucidated. They could depend on an interaction with the dopaminergic neurones from the cortex of *substantia nigra* and *striatum*, as well as with the serotonergic neurones of *locus ceruleus*. Morphine related substances might cause an excitation of certain neurones, particularly of pyramidal fibres from hippocampus, probably by inhibiting the release of GABA by interneurones.

Opioids act on the mechanisms of pituitary thermoregulation. At usual doses, they induce a diminution of rectal temperature. Conversely, at high dosages, they can provoke an augmentation of rectal temperature.

Opioid-induced nausea is due to a direct action on medullary chemoreceptors located in the "trigger zone" of the *area postrema*.

In the hypothalamus, morphine inhibits the liberation of GnRH (gonadotropin releasing hormone) and of CRF (corticotropin releasing factor), causing a diminution of the concentration in pituitary hormones (LH, FSH, ACTH and β -endorphin). Consequently, a reduction of plasma testosterone and in cortisol concentrations is observed. Moreover, the administration of μ type opioids induces an elevation in the concentration of prolactin, probably through an effect on the dopaminergic system.

A neuro-sympathetic action of opioids on eyes is expressed by a myosis and by a reduction of the intra-ocular pressure.

Finally at high doses, opioids may induce muscle rigidity that can cause respiratory difficulties, as well as an abnormal behaviour in animals. These effects are probably due to the action of these substances on the *substantia nigra* and the *striatum* and involve an interaction with the serotonergic and GABAergic systems.

Cardio-vascular system

In the recumbent position, morphine and related substances induce no modification of arterial blood pressure or heart rate. When getting into an upright position, orthostatic hypotension, possibly causing faintness, has been sometimes reported. This effect might be due to a massive histamine release, which causes peripheral arteriolar and venous vasodilatation.

Digestive tract

Stomach: morphine and other μ agonists generally reduce the secretion of hydrochloride acid, through a reduced production of somatostatin by the pancreas. Morphine, at low doses, reduces gastric motility and delays gastric emptying, which therefore enhances the risks of oesophageal reflux.

Small intestine: morphine reduces biliary, pancreatic and intestinal secretions and delays food digestion in the small intestine. Conversely, the amplitude of peristaltic waves is generally augmented but propulsive waves are reduced, the latter being the cause of constipation. Gallbladder: Morphine may provoke contractions of Oddi's sphincter thus causing epigastric pain

Genito-urinary system

At therapeutic doses, morphine may exert antidiuretic effects through a contraction of urethra. Moreover, it may extend the duration of labour during delivery.

Respiratory system

Opioids exert antitussive effects. This can be evidenced experimentally, on models of electrical excitation of the medulla or via mechanical or chemical irritation of the airways. In the case of codeine, the therapeutic dose that induces an antitussive action is lower than the analgesic dose. The action of codeine on cough depends on different receptors than those involved in its analgesic effects.

1.2.3 Relationship between plasma concentration and effect

Paracetamol

The usual therapeutic doses produce plasma concentrations of 5 to 20 µg/ml. Little is known of the concentration-effect relationship of paracetamol. As judged by pain relief scores, the onset and duration of analgesic activity corresponds approximately to the plasma concentration-time curve after oral administration of a therapeutic dose, and from such data it would appear that analgesia is associated with concentrations above 5 µg/ml.

Codeine

The relationship between plasma concentration and effect for codeine has not been detailed. However, as the analgesic effect of codeine is related to its metabolites including morphine and M6G there is unlikely to be a clear concentration-effect relationship for codeine

1.2.4 Pharmacodynamic interactions with other medicinal products or substances

Codeine potentiates the central depressive effects of central nervous system depressants, including alcohol, anxiolytics, hypnotics, antidepressants and antipsychotics. This harmful interaction has been experimentally demonstrated with the aid of a driving simulator measuring psychomotor skills²².

Due to its mechanism of action, concomitant administration of codeine and anticholinergics may cause paralytic ileus. Also, concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation, and coadministration with an antimuscarinic drug may cause urinary retention. The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated codeine. However, a thorough examination of the scientific literature did not reveal any contribution describing the interactions cited above.

There is some evidence that chronic, excessive consumption of alcohol may increase the risk of *paracetamol*-induced hepatotoxicity.

Genetic differences in pharmacodynamic response

See Section 1.1.3

²² Linnoila M, et al., 1973.

2. EFFICACY

1.1 Meta-analyses and main clinical studies

1.1.1 Surgical / Post-operative pain

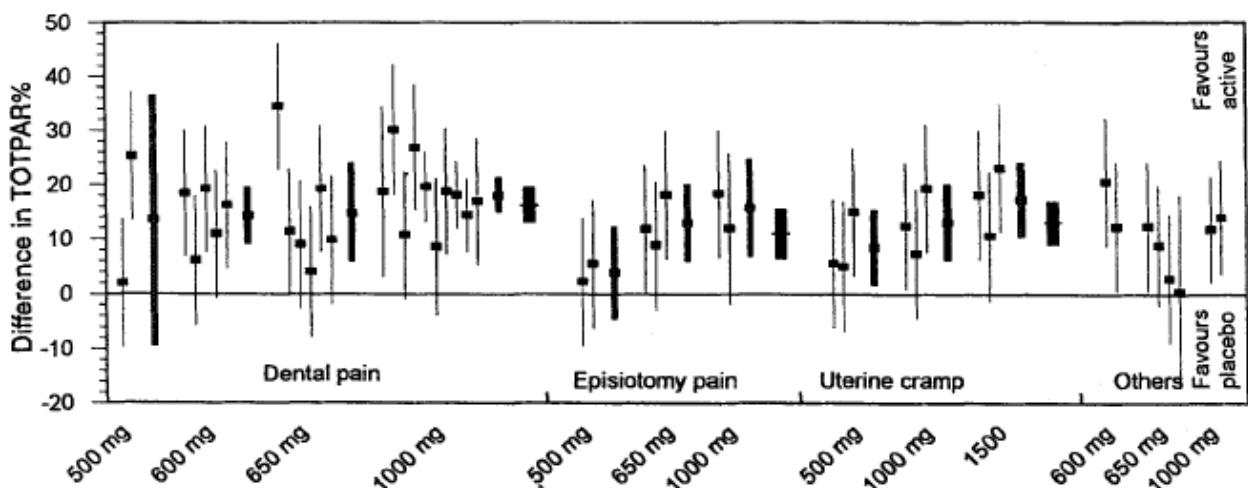
1.1.1.1. Meta-analysis 1 – Surgical Pain (Zhang WY et al 1996)

This meta-analysis included randomized controlled trials (RCTs) of paracetamol, identified through a search consisting of the MEDLINE and BIDS databases *over* the period 1966 to May 1996. Only studies evaluating the effects of single doses of conventional oral formulations of paracetamol were included in the meta-analysis. Studies dealing with postoperative acute pain, including dental pain (tooth extraction, dental bone removal, periodontal surgery) and postpartum pain (episiotomy, uterine cramp), orthopaedic surgery, general surgery, rectal surgery, hysterectomy, mastectomy, osteotomy and caesarean section were included.

Standardised %TOTPAR (total pain relief) and %SPID (summed pain intensity difference) outcomes were derived to take account of different scales used in different trials. Efficacy was also estimated using the response rate ratio (ResRR) for patients receiving the treatment relative to placebo. Response rate is defined as the proportion of patients reporting moderate to excellent or greater than 50% pain relief during the observation period. In addition, the re-medication rate ratio (RemRR) for patients receiving the treatment relative to placebo was also analysed. Re-medication rate is defined as the proportion of patients requiring rescue analgesics during the observation period.

In terms of % TOTPAR, % SPID, ResRR, RemRR the efficacy of paracetamol versus placebo was clearly demonstrated for all pain types assessed at all doses (600 mg, 650 mg, 1000 mg) except 500 mg, although even at the low dose there was a trend suggestive of positive effect. There was no obvious dose-response relationship. The rate ratio for pain relief and the rate ratio for re-medication confirmed paracetamol's analgesic efficacy.

Figure 1: Difference in TOTPAR% between paracetamol and placebo in various types of pain. Error bars refer to 95% CI. Individual result (line), pooled result (individual doses) (light shading), pooled result (all doses) (heavy shading).



With regards to the paracetamol/codeine combination versus paracetamol the point estimates suggest efficacy in favour of the codeine combination, but there was no statistical difference between the combination and monoproduct for individual comparisons, except for the 600 mg paracetamol plus 60 mg codeine compared to the 600 mg paracetamol comparison - See Figure 2 and Table 2.

Figure 2: Pooled difference in TOTPAR% for paracetamol (no shading), paracetamol+codeine (heavy shading) and paracetamol+caffeine (light shading) as compared to placebo. Error bars refer to 95% CI.

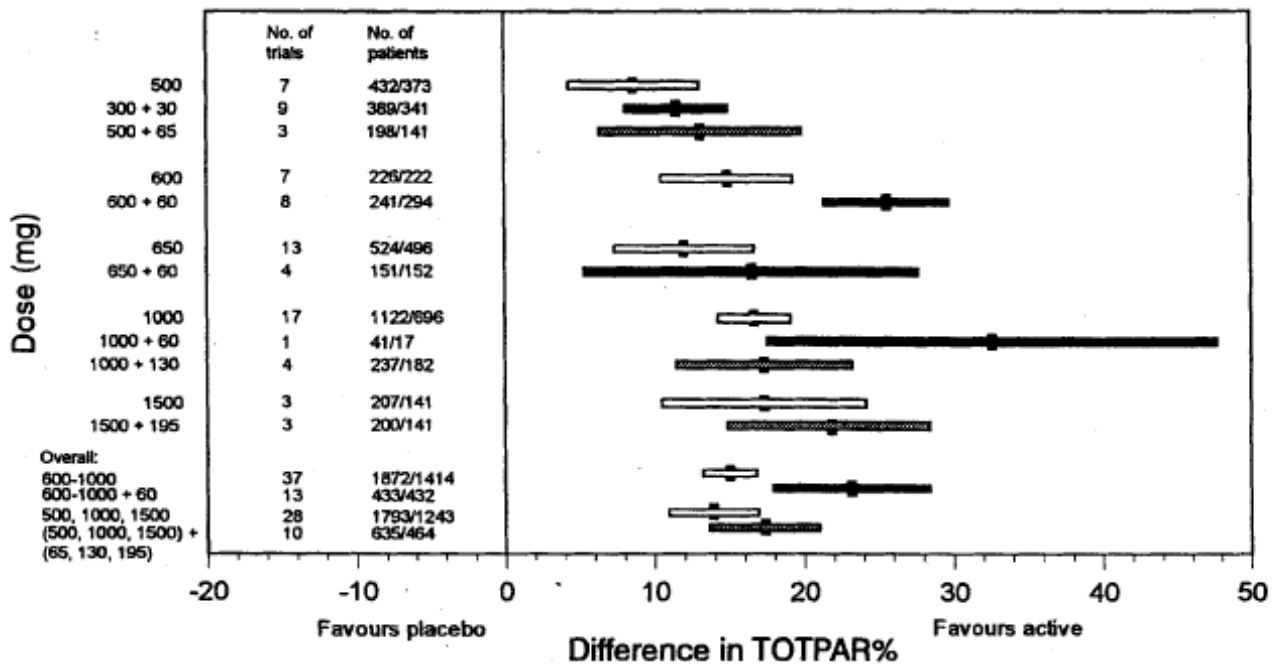


Table 2: Head-to-head comparisons of efficacy (difference in TOTPAR%) of the combinations versus paracetamol

Comparisons	No. of trials	No. of patients [▲]	TOTPAR%						
			Combination	Paracetamol	†d	SE	Z	95% CI	χ ² _{heter} [‡]
Paracetamol + codeine vs. paracetamol									
600+60 vs. 600	7	214/226	42.89	31.61	11.28	3.09	3.65¶	5.22, 17.23	13.33§
650+60 vs. 650	3	112/104	41.48	39.84	1.64	3.17	0.52	-4.56, 7.85	2.31
1000+60 vs. 1000	3	123/118	50.62	47.55	3.56	6.31	0.56	-8.82, 15.93	6.98§
Total	13	449/448	44.34	37.09	7.39	2.43	3.04¶	2.62, 12.16	30.00¶
Paracetamol + caffeine vs. paracetamol									
500+65 vs. 500	3	198/203	54.38	49.79	4.58	3.17	1.45	-1.62, 10.79	0.32
1000+130 vs. 1000	4	237/240	53.25	50.03	3.22	2.74	1.17	-2.18, 8.59	4.48
1500+190 vs. 1500	3	200/207	62.92	58.54	4.38	3.17	1.38	-1.83, 10.58	0.81
Total	10	635/650	56.49	52.51	3.97	1.73	2.29§	0.57, 7.37	5.73

[▲]The number of patients shown to the left of the solidus received the combination; the number shown to the right of the solidus received paracetamol alone.

†d is the difference in TOTPAR% between the combination and paracetamol.

‡χ²_{heter} is the chi-square statistic for heterogeneity. Where the results are heterogeneous, the random effects model was used to provide pooled interval estimates.

§P ≤ 0.05; ¶P ≤ 0.01.

The overall pooled estimates showed that combinations of 600-1000 mg paracetamol with 60 mg codeine were as a group superior to paracetamol on its own. Results for SPID were similar, i.e., there was no statistical difference between the combination and monoproducts, except for the 600 mg paracetamol plus 60 mg codeine compared to the 600 mg paracetamol, and for the pooled comparison of 600-1000 mg paracetamol with 60 mg codeine were as a group superior to paracetamol on its own. ResRR and RemRR did not show any superiority of the combination over paracetamol on its own.

Conclusion

In terms of the products and posology proposed for marketing, i.e., codeine/paracetamol 15/500 mg and 30/500 mg one to two tablets to be taken four-hourly as required, the following conclusions may be drawn:

The meta-analysis broadly supports the efficacy of a single dose of codeine/paracetamol 60/1000 (two tablets of 30/500 mg) over paracetamol 1000mg alone in post-surgical pain.

1.1.1.2. Meta-analysis 2 and 3 – Post-operative pain (Moore et al, 1997 and 1998)

The Oxford Pain Research Unit which published 2 meta-analyses in 1997 and 1998 in post-operative pain using very similar methods to one another. The 1997 meta-analysis included 31 trials of paracetamol against placebo (as opposed to 40 in meta-analysis 3), 19 (as opposed to 22) trials of paracetamol plus codeine against placebo and 13 (as opposed to 12) trials of paracetamol plus codeine against the same dose of paracetamol. The 1998 meta-analysis included published trials from Medline (1966 to May 1996), Embase (1980 to 1996), Cochrane Library (Issue 2 1996) and the Oxford Pain Relief Database (1950 to 1994). Additional trials were identified from reference lists of retrieved studies. Given the substantial overlap with the dates of studies including in Zhang et al's meta-analysis it is likely that many of the same studies were included in both analyses.

Inclusion criteria were: Full journal publication, postoperative pain, (post dental extraction, postsurgical or postpartum pain), postoperative oral administration, adult patients, baseline pain of moderate to severe intensity (for studies using a visual analogue scale (VAS), pain of at least moderate intensity equates to >30 mm), double-blind design, and random allocation to treatment groups which compared paracetamol with placebo or a combination of paracetamol and codeine with either placebo or the same dose of paracetamol alone. Multiple dose studies were included if the appropriate data from the first dose was available. In postpartum pain, trials were included if the pain investigated was due to episiotomy or caesarean section irrespective of the presence of uterine cramps but trials investigating pain due to uterine cramps alone were excluded.

The derived pain relief outcomes extracted were TOTPAR (total pain relief) or SPID (summed pain intensity difference) over 4 to 6 hours. These data were converted into dichotomous information to yield the number of patients with at least 50% pain relief. This was used to calculate the relative benefit (RB) and number-needed-to-treat (NNT) for one patient to achieve at least 50% pain relief over 4 to 6 hours compared with placebo. Adverse effects were used to calculate relative risk and number needed- to-harm (NNH).

40 trials fulfilled the inclusion criteria: 22 trials investigated oral surgery pain (postdental pain, predominantly third molar extraction with bone removal), 8 postsurgical (elective general, gynaecological and orthopaedic surgery) and 10 postpartum (episiotomy and Caesarean section).

40 trials of paracetamol against placebo (4171 patients), 22 trials of paracetamol plus codeine against placebo (1407 patients) and 12 trials of paracetamol plus codeine against the same dose of paracetamol (794 patients) were included.

Paracetamol 600/650 mg plus codeine 60 mg had an NNT of 3.6 for at least 50% pain relief compared with placebo in single dose administration, meaning that one in every four patients

with pain of moderate to severe intensity will get at least 50% pain relief, which they would not have had if they had been given a placebo.

There was only a slight overlap between the 95% confidence interval of the NNT for paracetamol 600/650 mg plus codeine 60 mg in 15 trials (2.9-4.5) and that of paracetamol 600/650 mg alone in 17 trials (4.1-7.2). This indirect comparison suggests that addition of codeine 60 mg provides an increase in analgesia in single dose administration. However, this may be accompanied by an increase in mild central nervous system adverse effects ('drowsiness' and 'dizziness'). The extra analgesic effect of adding codeine 60 mg to paracetamol was also estimated directly. For paracetamol plus codeine 60 mg versus the same dose of paracetamol (combining all doses of paracetamol) the NNT for at least 50% pain relief in single dose administration was 7.7 (5.1- 7). This means that for every eight patients given paracetamol plus codeine 60 mg, one extra will achieve at least 50% pain relief which they would not have experienced had they received paracetamol alone. This direct comparison did not indicate any increase in the incidence of adverse effects with the addition of codeine.

Conclusions

As per Zhang et al's meta-analysis, this meta-analysis supports the use of single doses of 1000/60 mg paracetamol/codeine in post-operative pain (synonymous with surgical pain), and confirms its greater efficacy than the same dose of paracetamol alone.

1.1.1.3 Meta-analysis 4 – Post-operative pain (Toms et al, 2009)

An updated version of the Cochrane meta-analysis published in 1998 (i.e., 'meta-analysis 3' above) was recently published 2 new studies comparing paracetamol/codeine versus the same dose of paracetamol alone, and 4 new studies of the combination versus placebo.

Randomised, double-blind, placebo-controlled trials of paracetamol plus codeine, compared with placebo or the same dose of paracetamol alone, for relief of acute postoperative pain in adults were considered. Twenty-six studies, with 2295 participants, were included comparing paracetamol plus codeine with placebo. Fourteen studies, with 926 participants, were included in the comparison of paracetamol plus codeine with the same dose of paracetamol alone. This update confirms previous findings that combining paracetamol with codeine provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain, compared with under 20% with placebo. New information for remedication shows that the combination extended the duration of analgesia by about one hour compared to treatment with the same dose of paracetamol alone. At higher doses, more participants experienced adequate pain relief.

1.1.1.4 Study 1 – Post-surgical pain (Gertzbein et al 1986)

This is one of two studies amongst the individual post-operative pain studies which compares the combination versus codeine alone.

Whilst this study was included in the meta-analysis 3, combination versus codeine effects were not estimated as part of the latter.

Gertzbein et al randomised 113 patients with at least moderate pain following general surgical or orthopaedic procedures to paracetamol 1000 mg, codeine phosphate 60 mg or paracetamol/codeine 1000/60 mg in a 2:1:2 ratio. The study medication was the first oral analgesic post-surgery usually after 24-48 hours of intramuscular pethidine. Pain intensity (using a VAS and 5-point ordinal scale) and pain relief were assessed for 5 hours after

administration of a single dose off study medication, which allowed the estimation of SPID and TOTPAR. Patients were allowed to request rescue medication in which case a LOCF approach was used.

Baseline characteristics (including pain intensity) were similar between groups. Results are presented in Table 4.

Table 3: SPID and TOTPAR results

	Paracetamol (n=45)	Codeine (n=23)	Paracetamol/ Codeine (n=45)
SPID, ordinal	3.69 (3.91)	2.52 (3.15)	4.54* (3.88)
SPID, VAS	8.04 (8.65)	2.68 (6.37)	11.22** (10.16)
TOTPAR	10.22 (6.21)	7.91 (4.58)	11.62* (6.48)

*p<0.05 vs codeine

**p<0.01 vs codeine

As can be seen in the table above, the study demonstrated that a single dose of the combination was superior to codeine alone.

Conclusions

This study supports the efficacy of a single dose of paracetamol/codeine 1000/60 mg over codeine 1000 mg, hence supports the use of two tablets of the higher dose product. Although the study did not confirm the superiority of a single dose of the combination (1000/60 mg) over paracetamol (1000 mg) alone that has been adequately demonstrated elsewhere.

1.1.1.5 Study 7 – Post-surgical pain (Bjune et al 1996)

This study was a randomized, double-blind, placebo-controlled single dose study in patients with moderate to ‘strong’ postoperative pain after caesarean section. Patients were randomised to paracetamol 1000 mg, paracetamol 800 mg plus codeine 60 mg, or placebo. Visual analogue pain intensity score (VAS 0-100 mm) and categorical pain relief score were recorded for 6 hours study drug intake. The main efficacy variables analyzed were: pain intensity difference and summed pain intensity differences during the first 3 and 6 h after study drug intake, total pain relief during the first 3 and 6 h, global evaluation score at the end of the observation period, and time to rescue analgesic. For the 108 patients included in the efficacy analysis results are presented below by ‘moderate pain’ (VAS 40 - 60 mm) and ‘strong pain’ (VAS > 60 mm) – note the table incorrectly describes the combination dose as 1000/60 rather than 800/60 mg. 49 patients had moderate baseline pain, and 59 patients had strong baseline pain.

Summary efficacy variables. Median values and 25th and 75th percentiles.

Group	n	SPID3h		SPID6h		TOTPAR3h		TOTPAR6h		Global evaluation	No. taking rescue drug/All	Time to rescue drug (max=6h)
<i>Strong baseline pain (VAS≥60 mm)</i>												
Paracetamol 1000	108			184		6.5		10.5		3		6
+ codeine 60 mg	21	27	126	84	243	4.5	7.5	7.5	11.5	1	3	6
		36		78		3.8		6.4		2		6
Paracetamol 1000	26	12	65	30	175	1.5	5.5	2.5	13	1	3	6
		2.5		-7.5		0		0		0		1.8
Placebo	12	-18	3	-42	2.75	0	0.3	0	0.3	0	0	6
						0		0		0		4.25
All three groups*						0.0002		0.0004		0.0001		0.0002
Para-cod vs Plac*						0.0002		0.0007		0.0002		0.0001
Para-cod vs Para*						0.02		0.04		0.02		0.05
Para vs Placebo*						0.005		0.002		0.003		0.001
										0.0003		0.0001
										0.0001		0.0001
										0.05		0.05
										0.01		0.001
										0.08**		0.001
<i>Moderate baseline pain (40 mm< VAS<60 mm)</i>												
Paracetamol 1000	23			24		37		4		6.5		6
+ codeine 60 mg	23	-11	92	-27	132	1.5	6.5	2	12.5	1	3	6
		29		60		3		8		1		6
Paracetamol 1000	17	2	64	-18	120	1.5	6.5	2	11.5	0	3	6
		17		10		1.5		1.5		1		6
Placebo	9	6	29	1	96	1	2	1	8	0	2	6
												3
All three groups*						NS		NS		NS		NS
												NS
												NS
												NS
												NS
												NS

*Kruskal-Wallis-test; **Fisher's exact test; P-values. For definitions of efficacy variables, see Patients and methods.

As can be seen above in patients with strong baseline pain, significant differences were noted between the active drugs and placebo and between the two active drugs (in favour of the combination product). However, in patients with moderate baseline pain, no difference between any treatment groups was noted.

This is a potentially important study as it supports the efficacy of the combination product in acute visceral pain models.

1.1.2 Dento-alveolar pain

In total 6 individual dental pain studies have been summarised by the Applicant in the Clinical Overview. Only those studies which add to the findings meta-analyses previously described (which included subjects with dental pain) will be detailed below.

1.1.2.1 Study 1– Dento-alveolar pain (Sunshine et al 1986)

This study was included in ‘meta-analysis 3’ and investigates the relative analgesic efficacy and safety of single oral doses of 50 and 100 mg of flurbiprofen were compared with 100 mg of zomepirac sodium, 650 mg of paracetamol plus 60 mg of codeine, 650 mg of paracetamol alone, and placebo in a randomized, double-blind, parallel-group study.

A total of 182 patients entered the study with moderate pain from a third molar extraction and were evaluated for six hours. Results are presented in the table below:

Table 4: Pain intensity, SPID, pain relief and TOTPAR results

Variable	Placebo (n = 30)	Acetaminophen (650 mg) (n = 30)	Acetaminophen (650 mg) plus Codeine (60 mg) (n = 31)	Zomeprae (100 mg) (n = 31)	Flurbiprofen (50 mg) (n = 31)	Flurbiprofen (100 mg) (n = 29)
Baseline pain intensity	2.00	2.00	2.00	2.00	2.00	2.00
Pain intensity difference						
.5 hour	0.30	0.60	0.71	0.90	0.61	0.41
1 hour	0.20	1.13*	1.32*	1.45*	1.23*	0.93*
2 hour	0.37	1.10*	1.13*	1.81* ^{†‡}	1.39*	1.35*
3 hour	0.43	1.07*	1.03*	1.74* ^{†‡}	1.45*	1.41*
4 hour	0.17	0.67	0.61	1.57* ^{†‡}	1.13*	1.17*
5 hour	0.23	0.33	0.48	1.07* ^{†‡}	1.13* ^{†‡}	1.17* ^{†‡}
6 hour	0.20	0.20	0.39	0.81	1.00* [†]	1.07* [†]
Sum of pain intensity difference						
4 hour	1.22	3.70*	3.79*	6.24* ^{†‡}	4.89*	4.60*
6 hour	1.65	4.23	4.66	8.11* ^{†‡}	7.01*	6.85*
Pain relief						
.5 hour	0.97	1.47	1.90	2.10	1.68	1.10
1 hour	1.17	2.50	3.10* [§]	3.13* [§]	2.84*	2.00
2 hour	1.53	2.43*	2.74*	3.71* ^{†‡}	3.10*	2.83*
3 hour	1.60	2.23	2.52	3.65* ^{†‡}	3.10*	3.00*
4 hour	1.43	1.77	2.10	3.19* [†]	2.61*	2.76*
5 hour	1.33	1.47	1.81	2.71* [†]	2.52* [†]	2.69* [†]
6 hour	1.37	1.20	1.71	2.55* [†]	2.58* [†]	2.62* [†]
Total pain relief						
4 hour	5.63	8.42	9.86*	13.16* ^{†‡}	11.07*	10.14*
6 hour	8.33	11.08	13.37	18.42* [†]	16.16* [†]	15.45*
Time to peak effect (minutes)	220.00	112.00*	114.19*	79.36*	120.97*	140.69*
Overall improvement	3.97	4.20	4.61	5.13*	5.22*	5.35* [†]
Overall impression of study drug	0.93	1.20	1.48	2.00* [†]	2.03* [†]	1.76*

*p ≤0.05, better than placebo.

†p ≤0.05, better than 650 mg of acetaminophen.

‡p ≤0.05, better than 650 mg of acetaminophen plus 60 mg of codeine.

§p ≤0.05, better than 100 mg of flurbiprofen.

For SPID4 (but not SPID6) both paracetamol and paracetamol/codeine were significantly superior to placebo. For TOTPAR4 only paracetamol/codeine was significantly superior to placebo ($p < 0.05$). Neither product differed from placebo in terms of cumulative pain intensity / relief indices at 6 hours. Finally there was no significant difference between the analgesic effects of paracetamol alone versus paracetamol /codeine.

This study supports the rationale for repeat dosing at 4 hours with paracetamol/codeine.

1.1.2.2 Study 2– Dento-alveolar pain (MacLeod AG et al 2002)

This randomized, double-blind parallel group trial compared paracetamol 1000 mg to paracetamol/codeine 1000/30 mg for the relief of pain following surgical removal of impacted third molars. Surgery was performed under local anaesthesia. After initial recording of post-operative pain at one hour, patients took the first dose of study medication. They were instructed to take two further doses of the study drug at four-hourly intervals, with the final dose to be taken eight hours after the initial dose. The change in VAS at 12 hours post-procedure was the primary measure of efficacy in this study. 79 of 82 patients randomized completed the trial. For the primary outcome patients receiving the paracetamol-codeine combination had a median increase in pain of 0.45cm/h, while in those receiving paracetamol alone the median increase in pain was 1.81cm/h. The median difference of 1.13cm/h (95% CI: 0.18 to 2.08cm/h) between the two treatment groups was statistically significant ($P=0.03$). Of the patients who received the paracetamol codeine combination, 62% used escape medication compared with 75% of those on paracetamol alone ($p=0.20$). No adverse events

(AE) were considered treatment related and the incidence of AEs (5-7%) was similar in both groups.

This is an important study as it supports the efficacy of two tablets of the Applicant's lower strength product (500/15mg) versus paracetamol alone.

1.1.2.3 Studies 3-6

These studies have not been summarised further as they do not add to the body of evidence in view of the principal efficacy requirements for this application.

1.1.2.4 Study 7 – Dento-alveolar pain (Quiding 1982)

This study was a double-blind, randomised trial in patients suffering from pain after removal of an impacted lower wisdom tooth. Patients were randomised to one of the following (up to 5 doses allowed);

- Paracetamol 500 mg
- Paracetamol 500 mg plus codeine 20 mg
- Paracetamol 500 mg plus codeine 30 mg
- Paracetamol 500 mg plus codeine 40 mg

Treatment	Tablet 1	
	Pain reduction	PRIX per tablet
Paracetamol [n = 66]	16% (- 35, 37)	43 (- 100, 110)
Paracetamol plus 20mg codeine [n = 67]	33% (- 24, 66)	100 (- 50, 338)
Paracetamol plus 30mg codeine [n = 65]	28% (- 49, 64)	85 (- 78, 275)
Paracetamol plus 40mg codeine [n = 68]	45% (4, 64)	150 (13, 369)

Side effects are presented below:

	Paraceta- mol	Paraceta- mol plus 20mg codeine	Paraceta- mol plus 30mg codeine	Paraceta- mol plus 40mg codeine
Concentration difficulties	-	-	1	-
Dizziness	1	4	2	4
Drowsiness	1	1	5	3
Gastric discomfort	1	-	-	1
Headache	1	-	1	2
Nausea	2	7	3	8
Restlessness	1	-	-	-
Weakness	-	1	1	1
No. of side-effects	7	13	13	19
No. of patients with side-effects	6 (9%)	8 (12%)	9 (14%)	15 (22%)

A statistically significant dose-response relationship was demonstrated using an analysis which considered repeat dose intake.

This study clearly demonstrated the benefits of the combination product over paracetamol alone. Dose response (for both efficacy and safety) was also clearly evident when comparing the 40 mg codeine dose with lower doses.

1.1.2.5 Study 8 – Dento-alveolar pain (Bentley KC et al 1987)

This was a double-blind, randomized, single-dose, 2 x 2 factorial design, parallel-group study to assess the analgesic contribution of paracetamol 1000 mg, and codeine 60 mg to the combination product. 120 patients suffering from pain as a result of oral surgery rated their pain intensity and pain relief for up to 5 hours after a single dose of one of the following:

- Paracetamol 1000 mg
- Codeine 60 mg
- Paracetamol 1000 mg plus codeine 60 mg
- Placebo

Patients who re-medicated before the fifth hour had their pain relief and pain intensity ratings at the time of re-medication carried over for the remaining time points in the statistical analysis.

Results are presented below:

<i>Treatment</i>	<i>Mean (SD)</i>				<i>Median time to re-medication (hr)</i>
	<i>PEAKPID</i>	<i>SPID</i>	<i>PEAKREL</i>	<i>TOTPAR</i>	
1000 mg Acetaminophen with 60 mg codeine	2.85 (2.32)	9.71 (10.49)	2.75 (1.07)	11.46 (5.01)	4.17
1000 mg Acetaminophen	2.20 (1.85)	6.17 (8.48)	2.32 (1.25)	8.68 (5.25)	3.25
60 mg Codeine	1.48 (2.71)	4.33 (11.80)	1.81 (1.36)	7.48 (5.58)	2.00
Placebo	-0.06 (2.95)	-2.00 (13.28)	1.25 (1.39)	4.94 (6.13)	1.47

The authors compared the effects of both monoproducts to placebo and demonstrated superiority to placebo for all endpoints above (statistical results not shown), demonstrating that both products contribute to the efficacy of the combination.

This study confirms the rationale for the combination. This study clearly suggests the potential superiority of the combination at a dose of 1000/60 over *both* monocomponents in acute surgical pain.

Conclusions

The efficacy of paracetamol/codeine 1000/60 has been demonstrated (meta-analyses, Gertzbein and a number of other individual studies)

The efficacy of paracetamol/codeine 1000/30 has been demonstrated (Macleod). Data from Gertzbein et al and Bentley et al suggests that paracetamol contributes the majority of the analgesic effect of the combination, hence superiority over paracetamol alone is considered acceptable.

Macleod et al's data suggest that addition of 30 mg codeine to 500 mg paracetamol (500/30) might confer additional benefit over paracetamol alone

There is evidence to support the rationale for repeat dosing at 4 hourly intervals (Turek, Sunshine)

The evidence presented relates to acute (post-surgical) pain. In this indication the efficacy of 30/500 – 60/1000 paracetamol/codeine has been adequately demonstrated. Posology of the 15/500mg tablets is 2 tablets to be taken four times a day (a total of 30/500) which is acceptable.

3. SAFETY

3.1 Adverse events

3.1.1 Meta-analyses

3.1.1.1 Meta-analysis 3 – Post-operative pain (Moore et al 1998)

This meta-analysis which evaluated primarily post-operative pain has been described previously. Safety of paracetamol/codeine 600-650/60 versus the same dose of paracetamol alone was briefly reported in the meta-analysis in addition to efficacy outcomes. Relative risk estimates were calculated for 'drowsiness'/'somnolence' (odds ratio 0.95 [95% CI 0.47, 1.94], 'dizziness' (1.13 [0.37, 3.42]) and 'nausea/vomiting' 2.08 [0.66, 6.57].

No significant difference was observed between paracetamol/codeine versus paracetamol alone for these three adverse events. Note that the studies included in this meta-analysis appear principally to be single-dose studies.

3.1.1.2 Meta-analysis 5 – Post-operative pain (de Craen et al 1998)

This meta-analysis incorporated a search of Medline (1964-95), International Pharmaceutical Abstracts (1965-91), and Biosis (1970-91) databases. Other publications were found by reviewing reference lists and by correspondence with manufacturers of paracetamol codeine preparations. Criteria for inclusion were (a) equal dosage of paracetamol in the paracetamol codeine and paracetamol only groups, (b) controlled clinical trial or randomised controlled trial, and (c) only codeine added to paracetamol (not caffeine).

Of twenty four studies included in the meta-analysis (for efficacy) 21 were of single dose design, all but two of which were postsurgical pain models. In most studies the treatment was taken when pain was moderate or severe. Of the 24 trials, six were excluded from the analysis of safety because they did not provide safety data or safety data were not categorised per treatment group. TABLE 8 gives the pooled safety results for 15 single dose and 3 multidose studies. No serious or unexpected adverse event was noted.

Table 8: Frequency of side effects in studies of paracetamol-codeine combinations versus paracetamol alone

Source	Paracetamol- codeine combination	Paracetamol	Pooled rate ratio (95% confidence interval)
Single dose studies (n = 15)			
No of patients reporting ≥1 event	484	488	1.1 (0.8 to 1.5)
No with adverse reaction	116	100	
No of events:			
Dizziness	14	11	
Drowsiness	39	35	
Nausea	18	17	
Vomiting	6	7	
Other	43	41	
Multidose studies (n = 3)			
No of patients reporting ≥1 event	307	164	2.5 (1.5 to 4.2)
No with adverse reaction	122	37	
No of events:			
Dizziness	42	2	
Drowsiness	12	2	
Nausea	69	9	
Vomiting	19	3	
Constipation	17	7	
Other	90	38	

The 15 single dose studies showed no significant difference between paracetamol/codeine combinations and paracetamol alone. The three multidose studies showed an increase in reported side effects with paracetamol-codeine. The frequency of dosing in the three studies was, respectively, two tablets three times a day, one tablet five times a day, and one tablet three times a day. In two studies side effects were reported on the first day, and in the remaining study they were reported during the first week.

Conclusion: The above data demonstrates that tolerability is best in the acute pain context and is less good with repeat dosing. Of note although tolerability treatment differences were much more overt with repeat dosing, note that these data were on the first day of multiple dosing in two of 3 cases, and in the first week in the third study.

3.2 Serious adverse events and deaths

In the studies analysed by the two cited meta-analyses, there were no serious adverse events which necessitated withdrawal from any study. No immunological events were apparent. No adverse effects were noted causing a serious medical condition or a prolonged hospitalisation. No fatal events were recorded.

In US monographs, it is stated that paracetamol may very rarely aggravate bronchospasm in patients who are sensitive to aspirin and other non-steroidal anti-inflammatory drugs (*no reports have been found in the medical literature*). It does not normally produce methaemoglobinemia or haemolysis, even after overdosage or in patients with dextrose-6-phosphate dehydrogenase deficiency.

3.3 Other significant adverse events

Because chronic, excessive consumption of alcohol may increase the risk of paracetamol-induced hepatotoxicity, chronic alcoholics are cautioned to avoid regular or excessive use of paracetamol, or alternatively, to avoid chronic ingestion of alcohol.

In the EU, the EMEA recently recommended withdrawal from the market of products containing paracetamol and dextropropoxyphene (Doc. Ref. EMEA/401061/2009) because of toxicity of the latter. No similar actions have been foreseen or undertaken for paracetamol and codeine combination products because this combination is regarded as safe in the approved indications.

3.4 Laboratory findings

Codeine interferes with some tests for estimating alkaloids, morphine and barbiturates in urine. In the range of concentrations associated with overdosage (hence, not during usual therapy), paracetamol may give a false positive result for plasma salicylate in tests based on the direct colour reaction with ferric ions. In the same circumstances it may induce spuriously high results for blood dextrose estimated with the YSI and Yellow Springs Model 23AM dextrose analyzers. Conversely, it may cause falsely low results for dextrose when the dextrose peroxidase/dextrose-6-phosphate dehydrogenase method is used.

3.5 Drug Abuse and Dependence (including Rebound Phenomenon)

Codeine shares the toxic potentials of the opiate agonists, and the usual precautions of opiate agonist therapy should be observed. Although psychological dependence on paracetamol may occur, tolerance and physical dependence do not appear to develop even with prolonged use.

3.6 Safety in special populations

3.6.1 Pregnancy

According to a survey of the US Collaborative Perinatal Project involving 1564 children born to mothers who were exposed to narcotic analgesics and possibly other drugs at some time during the first four months of the pregnancy, there is a possible association between respiratory malformations and codeine exposure. This agent should therefore be avoided as far as possible during pregnancy[1]. The expert has not found any pharmacoepidemiological signal of any adverse effects following the use of paracetamol in pregnancy, accessing the official Italian Pharmacovigilance Database. Recently, however, an international group of epidemiologists selected 66,445 women from the Danish National Birth Cohort for whom they had information on paracetamol use during pregnancy and who participated in an interview when their children were 18-months-old and 12,733 women whose children had reached the age of 7 and estimated the prevalence of physician-diagnosed asthma and wheezing at the ages of 18 months and 7 years. They also linked their population to the Danish National Hospital Registry to record all hospitalizations due to asthma up to age of 18 months. Paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months [relative risk (RR) = 1.17, 1.13-1.23], hospitalizations due to asthma up to 18 months (hazard ratio = 1.24, 1.11-1.38) and physician-diagnosed asthma at 7 years (RR = 1.15, 1.02-1.29). The highest risks were observed for paracetamol use during the first trimester of pregnancy and persistent wheezing (wheezing at both 18 months and 7 years) (RR = 1.45, 1.13-1.85) (Rebordosa C, et al., 2008).

3.6.2 Breastfeeding

Codeine should be used with caution in nursing women who are known or suspected ultrarapid metabolisers of cytochrome P-450 (CYP) 2D6 substrates. Although not routinely used in clinical practice and hardly available in Europe, an FDA-approved test (AmpliChip® CYP450 Test) is available to identify an individual's CYP2D6 genotype. Testing alone may not adequately predict the risk of adverse reactions; the decision to use codeine in nursing women should be based on clinical judgment. If used in such patients, codeine should be administered in the lowest effective dosage for the shortest possible time.

Paracetamol is distributed in human milk, although its concentration is 20% lower than in plasma. Scatchard analysis revealed high-affinity, low-capacity binding for paracetamol to pooled normal mature human milk *in vitro* (K_a [affinity constant of association], 1.47×10^4 L/mol; B_0 [concentration of binding sites], 9.01×10^{-4} mol/L) and some minimal, nonspecific binding. Binding ranged up to 85%. Binding of paracetamol to milk might enhance its excretion and subsequent ingestion by infants who are breast-fed. In addition, the low pH of the milk (6.24) may cause "ion trapping" of paracetamol (pK_a , 9.5) (Bailey DN, et al., 2004). For these reasons, paracetamol should be avoided during breast-feeding.

3.6.3 Children

The Applicant proposes that the fixed combination of paracetamol and codeine should not be administered in patients under the age of 18 years old.

3.6.4 Concomitant illnesses

Codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure. It should thus not be used in diverticulitis and following bowel surgery, or in patients with acute colitis.

Opioids must be used cautiously in patients with head injury. Although they may be required for analgesia, it should be borne in mind that they can depress respiratory function which can complicate respiratory difficulties associated with head injury. Carbon dioxide retention can cause dilatation of intracranial vessels and thus exacerbate cerebral oedema.

Hypovolemia can be exacerbated by codeine, so the drug should be used with caution in these circumstances (although there will be no medical reason to use such a fixed combination in an oral form in these latter patients).

Although some consider the use of paracetamol inadvisable in patients with liver disease, there is no evidence that it is harmful when taken in recommended doses. Paracetamol does not cause or aggravate chronic active hepatitis, and there was no deterioration in liver function in patients with chronic liver disease given 4 g of paracetamol daily for 13 days. Paracetamol is likely to be much safer than aspirin in patients with cirrhosis and portal hypertension.

Similarly, in patients with impaired renal function, paracetamol is less likely to cause further deterioration than the salicylates and other non-steroidal anti-inflammatory analgesics. As with other analgesics which inhibit prostaglandin synthesis, regular use should be avoided in patients with analgesic nephropathy.

3.7 Overdosage

Large doses of codeine produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur from respiratory failure. Blood concentrations of codeine ranged from 1.4 to 5.6 mg/l in eight adults whose deaths were attributed primarily to codeine overdosage. In a study on deaths related to codeine, the mean for suicide death was 1.2 mg/l; the persons involved were suffering from depressive mental illness and pain without addiction. Actually, this concentration could be reached by multiplying 60 mg per 10,000, which not feasible after the ingestion of the proposed products.

Because of its ready availability, paracetamol is often taken in overdose. The major complication is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (plasma aminotransferase > 1000 mg/l). About 1% develop fulminant hepatic failure which is usually fatal. Renal failure from acute tubular necrosis is a further uncommon complication which may develop in the absence of hepatic failure. There are no specific early manifestations of severe acetaminophen poisoning. Consciousness is not impaired except in the occasional unusually severely poisoned patients with metabolic acidosis, and maximum abnormality of liver function tests is delayed for at least 3 days. Emergency estimation of the plasma paracetamol concentration is therefore necessary to determine the severity of intoxication and the need for specific therapy with N-acetylcysteine. Without treatment, about 60% of patients with paracetamol concentrations above a line on a semilogarithmic graph joining plots of 200 mg/l at 4 h and 30 mg/l at 15 h after ingestion will suffer severe liver damage while above a parallel line joining 300 mg/l at 4 h and 45 mg/l at 15 h the chance is more than 90%.

Liver damage following overdose is relatively uncommon in young children. Paracetamol causes liver damage through its conversion to a highly reactive metabolite, and necrosis does not occur unless hepatic glutathione is depleted. Acetaminophen overdose, the leading cause of acute liver failure (ALF) in the United States, has a 66% chance of recovery with early N-acetylcysteine treatment and supportive care. Cerebral oedema and infectious complications are difficult to detect and treat in these patients and may cause irreversible brain damage and multiorgan failure. One-year survival after emergency liver transplantation is 70%, but 20% of listed patients die, highlighting the importance of early referral of patients who have ALF with a poor prognosis to a transplant centre (Fontana RJ, 2008).

3.8 Safety related to drug-drug interactions and other interactions

Interactions have been dealt with in the section 1.1.7 of this assessment report.

3.9 Post marketing experience/Risk management

The Applicant has submitted a PSUR for 3 paracetamol/codeine licences which it holds (Copaz Caplets [PL 12762/0056], Zapain Capsules [PL 12762/0033] and Zapain Caplets [PL 12762/0034]) covering the period 2002-2008. Some changes were apparently made to harmonise the SPC with that of the reference product. The Applicant has confirmed that any SPC changes referred to in the PSUR are reflected in the SPC for the proposed product.

3.10 Proposals for post authorisation follow up (post marketing surveillance)

No proposals for post-authorisation follow up were included, save for routine pharmacovigilance.

3.11 Overall conclusions on clinical safety

Overall safety has been adequately addressed. The 2 meta-analyses which have been summarised principally support product safety in the acute use context.

4. CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SPC, PIL and labelling are medically satisfactory.

6. APPLICATION FORM (MAA)

These are satisfactory.

7. CONCLUSION

The grant of these Marketing Authorisations is recommended for these applications.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Codipar 15mg/500mg and Zapain 30mg/500mg Effervescent Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new pre-clinical data were submitted and none are required for applications of this type.

CLINICAL

No new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required as these are 'well established use' applications.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol and codeine phosphate hemihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome