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LAY SUMMARY

The MHRA granted Consilient Health Ltd Marketing Authorisations (licences) for the medicinal products Codeine phosphate 15 mg, 30 mg and 60 mg tablets on 27 September 2011. These are prescription-only medicines (POM) used in:

- relief of mild to moderate pain
- symptomatic relief of coughing
- symptomatic relief of prolonged diarrhoea

Codeine phosphate belongs to a group of medicines called opioid analgesics. The action of codeine phosphate is largely that of morphine from which it is derived i.e it is a Central Nervous System (CNS) suppressant.

These applications are duplicates of previously granted applications for Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80), which were granted to the Marketing Authorisation Holder Ranbaxy Ireland Limited on 13 February 1990.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Codeine phosphate 15 mg, 30 mg and 60 mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
CODEINE PHOSPHATE 15 MG TABLETS
CODEINE PHOSPHATE 30 MG TABLETS
CODEINE PHOSPHATE 60 MG TABLETS

PL 24837/0023-5

SCIENTIFIC DISCUSSION

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Introduction Page 4
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Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Marketing Authorisations for the medicinal products Codeine phosphate 15 mg, 30 mg and 60 mg tablets (PL 24837/0023-5) to Consilient Health Ltd on 27 September 2011. These are prescription-only medicines (POM) indicated for use as an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.

Codeine phosphate belongs to a group of medicines called opioid analgesics. The action of codeine phosphate is largely that of morphine from which it is derived i.e it is a Central Nervous System (CNS) suppressant.

These applications were submitted as simple abridged applications according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80) approved on 13 February 1990 to the Marketing Authorisation Holder Ranbaxy Ireland Limited.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products.
1 INTRODUCTION
These are simple, informed consent applications for Codeine phosphate 15 mg, 30 mg and 60 mg tablets submitted under Article 10(c) of Directive 2001/83/EC. The applications cross-refer to Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80) approved on 13 February 1990, to Ranbaxy Ireland Limited.

The current applications are considered valid.

2 MARKETING AUTHORISATION APPLICATION (MAA)

2.1 Name(s)
The proposed names of the product are Codeine phosphate 15 mg, 30 mg and 60 mg tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains codeine phosphate 15 mg, 30 mg or 60 mg and is packaged in:

- polypropylene tamper-evident containers in pack sizes of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 500 and 1000 tablets
- blister strips in pack sizes of 10, 20, 28 (30 mg strength only) 30, 40, 50, 60, 70, 80, 90 and 100 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

The proposed shelf life is 3 years for the polypropylene tamper-evident containers and 2 years for the blister strips with the storage condition ‘Store below 25°C’.

The proposed shelf-life and storage conditions are consistent with the details registered for the cross-referenced products.

2.3 Legal status
On approval, the products will be available by supply through pharmacies, subject to a medical prescription (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
The proposed Marketing Authorisation Holder is Consilient Health Ltd, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland.

The Qualified Person (QP) responsible for pharmacovigilance is stated and their CV is included.
2.5 Manufacturers
The proposed manufacturing site is consistent with that registered for the reference products and evidence of compliance with current Good Manufacturing Practice has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the reference products.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in line with the details registered for the reference products.

2.9 Drug substance specification
The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

This is consistent with the reference products.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the reference products Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80).

3 EXPERT REPORT
The applicant has included a detailed pharmaceutical expert report, written by an appropriately qualified person.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to that of the reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPCs are consistent with the details registered for the reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING PIL
The patient information leaflet has been prepared in line with the details registered for the reference products.

Ranbaxy Ireland Limited has previously submitted results with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, for the reference products Codeine...
Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80). The results indicate that the leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patient/users are able to act upon the information that it contains.

As the leaflet for Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80) and these products are considered the same, no further user testing of the leaflet for these products is necessary.

Carton and blister
The proposed artwork complies with the relevant statutory requirements. In line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with these applications is acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As these applications are identical to the reference products Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80), no new non-clinical data have been supplied with these applications and none are required. A non-clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As these applications are for identical versions of already authorised reference products, it is not expected that the environmental exposure to codeine phosphate will increase following the marketing approval of the proposed products.
CLINICAL ASSESSMENT

As these applications are identical to the reference products Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80), no new clinical data have been supplied with these applications and none are required. A clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder 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.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the reference products and as such have been judged to be satisfactory.

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

EFFICACY
These applications are identical to the previously granted applications for Codeine Phosphate Tablets BP 15 mg, 30 mg and 60 mg (PL 06809/0078-80), granted to Ranbaxy Ireland Limited on 13 February 1990.

SAFETY
No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products.

Colour mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements. The name of the product in Braille appears on the outer packaging.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the reference products. Extensive clinical experience with codeine phosphate is considered to have demonstrated the therapeutic values of the compound. The benefit/risk is therefore considered to be positive.
**CODEINE PHOSPHATE 15 MG TABLETS**  
**CODEINE PHOSPHATE 30 MG TABLETS**  
**CODEINE PHOSPHATE 60 MG TABLETS**

**PL 24837/0023-5**

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**STEPS TAKEN FOR ASSESSMENT**

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<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 04 February 2009</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 24 February 2009</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 29 April 2009, 22 February 2010 and 29 March 2011</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 24 December 2009, 12 June 2010 and 01 September 2011</td>
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<td>5</td>
<td>The applications were determined on 27 September 2011.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Codeine phosphate 15 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 15 mg of codeine phosphate.
Excipient:
Each tablet contains 28.85 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White circular normal biconvex tablets, embossed with R114.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Recommended Uses: As an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.

4.2 Posology and method of administration
For oral administration.
As an analgesic:
Adults: 30-60mg every four hours, when necessary to a maximum 240mg daily.
Children: Not applicable.

As an anti-tussive:
Adults: 15-30mg three or four times daily.
Not recommended for children.

For the symptomatic treatment of chronic diarrhoea:
Adults: 10-60mg every four to six hours.
Children: Not applicable.
In general dosage should be reduced in elderly patients.

4.3 Contraindications
hypersensitivity to codeine phosphate, other opioid analgesics or any other of the excipients
patients with respiratory depression, liver disease, raised intracranial pressure, head injuries, acute alcoholism
and diarrhoea associated with either pseudomembranous colitis or poisoning.

4.4 Special warnings and precautions for use
Prolonged use of high doses has produced drug dependence of the Morphine type. Codeine should be used
with caution in patients with a history of drug dependence, in asthmatics and in patients with renal
impairment. Care should be taken if the patient has hypotension, hypothyroidism, adrenocortical insufficiency,
prostatic hypertrophy, acute abdominal conditions, recent GI surgery, gallstones, myasthenia gravis, history of
cardiac arrhythmias or convulsions.

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

Codeine Phosphate Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the
Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The leaflet will state in a prominent position in the “before taking” section:

Do not take for longer than directed by your prescriber.
Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets. Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack – not boxed):

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

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimates indicate that up to 7% of the caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers.

The leaflet will state in the “Pregnancy and breast-feeding” subsection of section 2 “Before taking your medicine”:

Usually it is safe to take “brand name” while breast feeding as the level of the active ingredients of this medicine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice; feeling sick, vomiting, constipation, decreased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

4.5 Interaction with other medicinal products and other forms of interaction
Forms codeine-phenobarbital complex with phenobarbital sodium and crystals of codeine periodide with potassium iodide. Codeine is known to interact with other CNS depressants (e.g. alcohol, sedatives, hypnotics), other antidiarrhoeal agents, neuromuscular blocking agents, antihypertensives, cimetidine and monoamine oxidase inhibitors (also within two weeks of stopping treatment with MAOI). Codeine also interferes with some laboratory tests e.g. plasma amylase, lipase, bilirubin.

4.6 Fertility, pregnancy and lactation
Not recommended during pregnancy due to neonatal withdrawal symptoms and impaired effect of foetus.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.

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

4.7 Effects on ability to drive and use machines
In combination with alcohol, it has a deleterious effect on driving.

4.8 Undesirable effects
Tolerance and dependence, sedation, dizziness, nausea and constipation commonly occurs. May enhance the effect of alcohol. Other undesirable effects are sweating, facial flushing, dry mouth, blurred or double vision, hypotension, malaise, headache, anorexia, bradycardia, allergic reactions (itch, skin rash, facial oedema) and difficulty in micturition. Rare side effects are convulsions, hallucinations, nightmare, uncontrolled muscle movements and rigidity, mental depression and stomach cramps.

Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped. Prolonged use of a painkiller for headaches can make them worse.
4.9 **Overdose**
The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

**Symptoms**
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

**Management** should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg or a child more than 5mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Opium alkaloids and derivatives, codeine
ATC code: R05DA04

The action of codeine is largely that of Morphine from which it is derived i.e. it is a CNS suppressant.

5.2 **Pharmacokinetic properties**
Codeine is metabolised in the liver and is excreted in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered Codeine is demethylated to form Morphine; traces of free morphine can be found in the urine after therapeutic doses of codeine.

5.3 **Preclinical safety data**
Animal work suggested that the analgesic activity of Codeine was not affected by Acetylation.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Lactose  
Starch  
Magnesium Stearate  
Sodium Starch Glycolate

6.2 **Incompatibilities**
None stated.

6.3 **Shelf life**
3 years: Polypropylene tamper-evident containers.  
2 years: Blister strips.

6.4 **Special precautions for storage**
Store below 25ºC.

6.5 **Nature and contents of container**
Polypropylene tamper-evident containers: 1000, 500, 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets  
Blister strips: 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets.

Not all pack types or sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Consilient Health Ltd.
MARKETING AUTHORIZATION NUMBER(S)
PL 24837/0023

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
27/09/2011

DATE OF REVISION OF THE TEXT
27/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Codeine phosphate 30 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 30 mg of codeine phosphate.

Excipient:
Each tablet contains 38.46 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White circular normal biconvex tablets, embossed with R115.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Recommended Uses: As an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.

4.2 Posology and method of administration
For oral administration.

As an analgesic:
Adults: 30-60mg every four hours, when necessary to a maximum 240mg daily.
Children: Not applicable.

As an anti-tussive:
Adults: 15-30mg three or four times daily.
Not recommended for children.

For the symptomatic treatment of chronic diarrhoea:
Adults: 10-60mg every four to six hours.
Children: Not applicable.

In general dosage should be reduced in elderly patients.

4.3 Contraindications
hypersensitivity to codeine phosphate, other opioid analgesics or any other of the excipients
patients with respiratory depression, liver disease, raised intracranial pressure, head injuries, acute alcoholism
and diarrhoea associated with either pseudomembranous colitis or poisoning.

4.4 Special warnings and precautions for use
Prolonged use of high doses has produced drug dependence of the Morphine type. Codeine should be used
with caution in patients with a history of drug dependence, in asthmatics and in patients with renal
impairment. Care should be taken if the patient has hypotension, hypothyroidism, adrenocortical insufficiency,
prostatic hypertrophy, acute abdominal conditions, recent GI surgery, gallstones, myasthenia gravis, history of
cardiac arrhythmias or convulsions.

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

Codeine Phosphate Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the
Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The leaflet will state in a prominent position in the “before taking” section:

Do not take for longer than directed by your prescriber.
Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and
irritable when you stop the tablets.
Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack – not boxed):

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

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimates indicate that up to 7% of the caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers.

The leaflet will state in the “Pregnancy and breast-feeding” subsection of section 2 “Before taking your medicine”:

Usually it is safe to take “brand name” while breast feeding as the level of the active ingredients of this medicine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice; feeling sick, vomiting, constipation, decreased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

4.5 Interaction with other medicinal products and other forms of interaction
Forms codeine-phenobarbital complex with phenobarbital sodium and crystals of codeine periodide with potassium iodide. Codeine is known to interact with other CNS depressants (e.g. alcohol, sedatives, hypnotics), other antidiarrhoeal agents, neuromuscular blocking agents, antihypertensives, cimetidine and monoamine oxidase inhibitors (also within two weeks of stopping treatment with MAOI). Codeine also interferes with some laboratory tests e.g. plasma amylase, lipase, bilirubin.

4.6 Fertility, pregnancy and lactation
Not recommended during pregnancy due to neonatal withdrawal symptoms and impaired effect of foetus.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.

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

4.7 Effects on ability to drive and use machines
In combination with alcohol, it has a deleterious effect on driving.

4.8 Undesirable effects
Tolerance and dependence, sedation, dizziness, nausea and constipation commonly occurs. May enhance the effect of alcohol. Other undesirable effects are sweating, facial flushing, dry mouth, blurred or double vision, hypotension, malaise, headache, anorexia, bradycardia, allergic reactions (itch, skin rash, facial oedema) and difficulty in micturition. Rare side effects are convulsions, hallucinations, nightmare, uncontrolled muscle movements and rigidity, mental depression and stomach cramps.

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

Prolonged use of a painkiller for headaches can make them worse.
4.9 **Overdose**
The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

**Symptoms**
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

**Management** should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg or a child more than 5mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Opium alkaloids and derivatives, codeine  
ATC code: R05DA04

The action of codeine is largely that of Morphine from which it is derived i.e. it is a CNS suppressant.

5.2 **Pharmacokinetic properties**
Codeine is metabolised in the liver and is excreted in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered Codeine is demethylated to form Morphine; traces of free morphine can be found in the urine after therapeutic doses of codeine.

5.3 **Preclinical safety data**
Animal work suggested that the analgesic activity of Codeine was not affected by Acetylation.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Lactose  
Starch  
Magnesium Stearate  
Sodium Starch Glycolate

6.2 **Incompatibilities**
None stated.

6.3 **Shelf life**
3 years: Polypropylene tamper-evident containers.  
2 years: Blister strips.

6.4 **Special precautions for storage**
Store below 25ºC.

6.5 **Nature and contents of container**
Polypropylene tamper-evident containers: 1000, 500, 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets  
Blister strips: 100, 90, 80, 70, 60, 50, 40, 30, 28, 20 and 10 tablets.

Not all pack types or sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Consilient Health Ltd.,
8 MARKETING AUTHORISATION NUMBER(S)
PL 24837/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/09/2011

10 DATE OF REVISION OF THE TEXT
27/09/2011
1 NAME OF THE MEDICINAL PRODUCT
Codeine phosphate 60 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 60 mg of codeine phosphate.

Excipient:
Each tablet contains 76.92 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White circular normal biconvex tablets, embossed with R117.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Recommended Uses: As an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhoea.

4.2 Posology and method of administration
For oral administration.

As an analgesic:

Adults: 30-60mg every four hours, when necessary to a maximum 240mg daily.
Children: Not applicable.

As an anti-tussive:

Adults: 15-30mg three or four times daily.
Not recommended for children.

For the symptomatic treatment of chronic diarrhoea:

Adults: 10-60mg every four to six hours.
Children: Not applicable.

In general dosage should be reduced in elderly patients.

4.3 Contraindications
hypersensitivity to codeine phosphate, other opioid analgesics or any other of the excipients
patients with respiratory depression, liver disease, raised intracranial pressure, head injuries, acute alcoholism
and diarrhoea associated with either pseudomembranous colitis or poisoning.

4.4 Special warnings and precautions for use
Prolonged use of high doses has produced drug dependence of the Morphine type. Codeine should be used
with caution in patients with a history of drug dependence, in asthmatics and in patients with renal
impairment. Care should be taken if the patient has hypotension, hypothyroidism, adrenocortical insufficiency,
prostatic hypertrophy, acute abdominal conditions, recent GI surgery, gallstones, myasthenia gravis, history of
cardiac arrhythmias or convulsions.

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

Codeine Phosphate Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the
Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The leaflet will state in a prominent position in the “before taking” section:

Do not take for longer than directed by your prescriber.
Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and
irritable when you stop the tablets.
Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack – not boxed):

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

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimates indicate that up to 7% of the caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers.

The leaflet will state in the “Pregnancy and breast-feeding” subsection of section 2 “Before taking your medicine”:

Usually it is safe to take “brand name” while breast feeding as the level of the active ingredients of this medicine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice; feeling sick, vomiting, constipation, decreased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

4.5 Interaction with other medicinal products and other forms of interaction
Forms codeine-phenobarbital complex with phenobarbital sodium and crystals of codeine periodide with potassium iodide. Codeine is known to interact with other CNS depressants (e.g. alcohol, sedatives, hypnotics), other antidiarrhoeal agents, neuromuscular blocking agents, antihypertensives, cimetidine and monoamine oxidase inhibitors (also within two weeks of stopping treatment with MAOI). Codeine also interferes with some laboratory tests e.g. plasma amylase, lipase, bilirubin.

4.6 Fertility, pregnancy and lactation
Not recommended during pregnancy due to neonatal withdrawal symptoms and impaired effect of foetus.

At normal therapeutic doses codeine and its active metabolites may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.

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

4.7 Effects on ability to drive and use machines
In combination with alcohol, it has a deleterious effect on driving.

4.8 Undesirable effects
Tolerance and dependence, sedation, dizziness, nausea and constipation commonly occurs. May enhance the effect of alcohol. Other undesirable effects are sweating, facial flushing, dry mouth, blurred or double vision, hypotension, malaise, headache, anorexia, bradycardia, allergic reactions (itch, skin rash, facial oedema) and difficulty in micturition. Rare side effects are convulsions, hallucinations, nightmare, uncontrolled muscle movements and rigidity, mental depression and stomach cramps.

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

Prolonged use of a painkiller for headaches can make them worse.
4.9 **Overdose**
The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

**Symptoms**
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350mg or a child more than 5mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

5 **PHARMACOLOGICAL PROPERTIES**
5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Opium alkaloids and derivatives, codeine
ATC code: R05DA04

The action of codeine is largely that of Morphine from which it is derived i.e. it is a CNS suppressant.

5.2 **Pharmacokinetic properties**
Codeine is metabolised in the liver and is excreted in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered Codeine is demethylated to form Morphine; traces of free morphine can be found in the urine after therapeutic doses of codeine.

5.3 **Preclinical safety data**
Animal work suggested that the analgesic activity of Codeine was not affected by Acetylation.

6 **PHARMACEUTICAL PARTICULARS**
6.1 **List of excipients**
Lactose
Starch
Magnesium Stearate
Sodium Starch Glycolate

6.2 **Incompatibilities**
None stated.

6.3 **Shelf life**
3 years: Polypropylene tamper-evident containers.
2 years: Blister strips.

6.4 **Special precautions for storage**
Store below 25ºC.

6.5 **Nature and contents of container**
Polypropylene tamper-evident containers: 1000, 500, 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets
Blister strips: 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets.

Not all pack types or sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Consilient Health Ltd.,
5th Floor, Beaux Lane House, 
Mercer Street Lower, 
Dublin 2, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 24837/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/09/2011

10 DATE OF REVISION OF THE TEXT
27/09/2011
PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Codeine phosphate 15 mg tablets
Codeine phosphate 30 mg tablets
Codeine phosphate 60 mg tablets
(codine phosphate)

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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Codeine phosphate tablets are and what they are used for
2. Before you take Codeine phosphate tablets
3. How to take Codeine phosphate tablets
4. Possible side effects
5. How to store Codeine phosphate tablets
6. Further information

1. WHAT CODEINE PHOSPHATE TABLETS ARE AND WHAT THEY ARE USED FOR

Codeine phosphate tablets belong to a group of medicines called opioid analgesics.

Codeine phosphate tablets are used in:
- relief of mild to moderate pain
- symptomatic relief of coughing
- symptomatic relief of prolonged diarrhea

2. BEFORE YOU TAKE CODEINE PHOSPHATE TABLETS

Do not take Codeine phosphate tablets if:
- you know that you are allergic to Codeine phosphate, other opioid pain killers or any of the other ingredients
  (refer to section 6 below)
- you have just had a head injury
- you suffer from any of the following:
  - liver disease
  - severe breathing problems
  - neck stiffness
  - acute alcoholism
  - diarrhea associated with either severe inflammation of the bowel or poisoning.

Tell your doctor or pharmacist before taking Codeine phosphate Tablets if:
- you are taking monoamine oxidase inhibitors (MAOIs) or have been taking them within the last two weeks, MAOIs such as phenelzine or isocarboxazid, are medicines used to treat depression.
- you have a history of drug dependence, irregular heartbeat or convulsions.
- you have recently undergone gastro-intestinal surgery.
- you have been diagnosed as suffering from any of the following:
  - low blood pressure
  - deficiency in the activity of the thyroid gland
  - enlarged prostate
  - acute abdominal conditions
  - jaundice
  - severe weakness of muscles
  - asthma
  - reduced function of the adrenal gland, e.g. Addison's disease
- you have kidney problems, because the dose might need to be lower.

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.

Codeine is known to interfere with some medicines. It is particularly important to tell your doctor or pharmacist if you are taking the following medicines:
- MAOIs used to treat depression (refer to "Take special care in section 2 above")
- Phensulphentone
- Potassium oxide
- Sedatives
- Antidepressants and alcohol
- Other anti-diarrheal agents
- Non-steroidal anti-inflammatory agents
- Anti-hypertensives
- Cimetidine

Laboratory test results may also be affected.

Taking Codeine phosphate tablets with food and drink
Do not drink alcohol whilst taking Codeine phosphate tablets.

Alcohol may increase the sedative effects of Codeine phosphate tablets and make you very sleepy. You can also take the tablets regardless of food intake.

Pregnancy and breast-feeding
Do not use this medicine if you are pregnant.

Usually it is safe to take Codeine phosphate tablets while breast feeding as the level of the active ingredients of this medicine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice: feeling sick, vomiting, constipation, increased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or operate machinery because you may suffer from dizziness. This can affect driving or the operation of machinery.

Important information about Codeine phosphate tablets
- Do not take for longer than directed by your prescriber.
- Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.
- Taking a painkiller for headaches too often or for too long can make them worse.
Important Information about some of the ingredients of Codeine phosphate tablets
This medicine contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CODEINE PHOSPHATE TABLETS

Always take Codeine phosphate tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

For the relief of mild to moderate pain:
Adults: 30-60 mg every four hours, when necessary to a maximum of 240 mg daily.

For the relief and prevention of coughing:
Adults: 15-30 mg three or four times daily.

For the treatment of prolonged diarrhoea:
Adults: 10-60 mg every four to six hours.

Codeine phosphate tablets are not recommended for children. A lower dosage may be needed if you are elderly. Swallow these tablets with water.

If you take more Codeine phosphate tablets than you should
If you take too many tablets contact your doctor or pharmacist at once for advice.

If you forget to take Codeine phosphate tablets
Do not take a double dose to make up for a forgotten dose. Skip the missed dose and take the next tablet at the usual time.

If you stop taking Codeine phosphate tablets
Prolonged use can lead to tolerance and dependence on the medicine. Taking codeine regularly for a long time can be habit forming, which might cause you to feel restless and irritable when you stop the tablets. Your doctor will stop your tablets gradually to avoid you having withdrawal symptoms.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Codeine phosphate tablets can cause side effects, although not everybody gets them.

If the following happens, stop taking Codeine phosphate tablets and tell your doctor immediately or contact the casualty department at your nearest hospital:
- Allergic reactions (itch, skin rash, facial oedema)
- Convulsions
Possible undesirable effects are:
- Sedation
- Dizziness
- Feeling sick (nausea)
- Constipation
Other possible frequent undesirable effects are:
- Sweating
- Facial flushing
- Dry mouth
- Blurred or double vision
- Low blood pressure
- Malaise (general discomfort)
- Headache
- Loss of appetite
- Slow heart beat
- Difficulty in passing water

Rare side effects are:
- Hallucinations
- Nightmares
- Uncontrolled muscle movements and rigidity
- Mental depression
- Stomach cramps

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

5. HOW TO STORE CODEINE PHOSPHATE TABLETS

Keep out of the reach and sight of children.

Do not use Codeine phosphate tablets after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Store below 25°C. Store the tablets in the original packaging. Do not put them in another container.

For container packaging, replace the cap securely after use.

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

6. FURTHER INFORMATION

What Codeine phosphate tablets contain:
- The active substance is codeine phosphate. Each tablet contains: 15 mg, 30 mg or 60 mg of codeine phosphate.
- The other ingredients are lactose, starch, magnesium stearate and sodium starch glycollate.

What Codeine phosphate tablets look like and contents of the pack
Codeine phosphate 15 mg tablets are white, circular normal bionovex tablets embossed with R114
Codeine phosphate 30 mg tablets are white, circular normal bionovex tablets embossed with R115
Codeine phosphate 60 mg tablets are white, circular normal bionovex tablets embossed with R117

The tablets are available in 15 mg, 30 mg and 60 mg strengths and in containers of 1000, 500, 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets and in blister strips of 100, 90, 80, 70, 60, 50, 40, 30, 20 and 10 tablets. The 30 mg strength is also available in blister strips of 28 tablets.

Marketing Authorisation Holder:
Consilient Health Ltd.,
5th Floor, Beacon Lane House,
Merer Street Lower, Dublin 2,
Ireland

Manufacturer:
Ranbaxy Ireland Ltd.,
Sparfield, Cork Road, Cashel,
Co. Tipperary,
Ireland.

This leaflet was last revised in July 2011

MHRA PAR-Codeine phosphate 15 mg, 30 mg and 60 mg tablets

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Carton:

Each tablet contains 15 mg codeine phosphate. Read the enclosed leaflet before use. Use as directed by your doctor. Contains lactose. See leaflet for further information.

For oral use. Store below 25°C.

Keep out of the reach and sight of children.

Warning: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drinks.

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

MHRA PAR-Codeine phosphate 15 mg, 30 mg and 60 mg tablets
Blister:
Blister:
Carton:

Each tablet contains 40 mg codeine phosphate. Read the enclosed leaflet before use. Use as directed by your doctor. Contains lactose. See leaflet for further information. For oral use. Store below 25°C. Keep out of the reach and sight of children.

Warning: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drinks.

MA Holder: Consilient Health Ltd., 5th Floor, Beauch Lane House, Mercer Street Lower, Dublin 2, Ireland

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