1.4 PRODUCT INFORMATION

1.4.1. Prescribing Information (Summary of Products Characteristics)

1. Name of the finished Pharmaceutical Product

VERCOD (Codeine Phosphate Tablets BP 30 mg)

1.1 Strength: 30mg **1.2 Pharmaceutical form:** Uncoated tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration:

Each uncoated tablets contains

Codeine Phosphate BP…… 30mg

Excipients …… q.s.

2.2 Quantitative declaration:

Each uncoated tablets contains

Codeine Phosphate BP…… 30mg

Excipients …… q.s.

For full list of excipients see section 6.1.

2.3 Salts and hydrates:

VERCOD (Codeine Phosphate Tablets BP 30 mg)

2.4 Esters and pro-drugs

Not Applicable

2.5 Multi dose solid or semi-solid products

30mg

2.6 Biological medicinal products

Not Applicable

2.6.1 Expression of strength

Not Applicable

2.6.2 The biological origin of the active substance

Not Applicable

2.6.3 Special provisions for normal immunoglobulins

Not Applicable

2.6.4 Herbal pharmaceutical products

Not Applicable

3. PHARMACEUTICAL FORM

Uncoated Tablets

White round flat, uniscored uncoated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in adults as an analgesic, an anti-tussive, and for the symptomatic treatment of chronic diarrhea. Codeine is indicated in patients older than 12 years for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine phosphate in order to minimise the risk of addiction and drug withdrawal syndrome.

Posology

As an analgesic:

Adults: 30-60mg every four hours, when necessary to a maximum 240mg daily.

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

As an anti-tussive

Adults: 15-30mg three or four times daily.

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

For the symptomatic treatment of chronic diarrhoea:

Adults: 15-60mg every four to six hour

Elderly: Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240mg.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Paediatric population

Children over 12 years

30-60mg every four hours, when necessary to a maximum 240mg daily.

Children aged 12 years to 18 years

Codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and/or cold.

4.2 Method of Administration

For oral use

4.3 Contraindications Patients

with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Acute respiratory depression;
- Obstructive airways disease e.g. emphysema;
- Asthma – Opioids should not be administered during an asthma attack, hepatic failure;
- Head injuries or conditions where intracranial pressure is raised;

- -Acute alcoholism;
- Diarrhoea associated with either pseudomembranous colitis or poisoning; Risk of paralytic ileus.

This product is also contraindicated

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and lifethreatening adverse reactions.

In children below the age of 12 years for the symptomatic treatment of cough and/or cold due to an increased risk of developing serious and life-threatening adverse reactions.

In women during breastfeeding

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

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder.

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with codeine phosphate.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Codeine Phosphate Tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Codeine Phosphate Tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will

not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below

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

Post-operative use in children

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

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Codeine phosphate should be used with caution in the following conditions:

- There is a possible risk of CNS excitation or depression with concomitant use of opioids with Monoamine Oxidase Inhibitors (MAOIs) and use is not recommended.

Drug abuse or dependence (including alcoholism)

Pregnancy and breast feeding (see section 4.6)

- Convulsions – they may be induced or exacerbated
- Myasthenia gravis
- Phaeochromocytoma – opiods may stimulate catecholamine release by inducing the release of endogenous histamine
- Adrenocortical insufficiency e.g. Addison's Disease
- Hypothyroidism
- Hypotension and shock
- Reduced respiratory function or history of asthma
- Inflammatory bowel disease – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure, therefore should be used with caution in diverticulitis, acute colitis, diarrhoea associated with pseudomembranous colitis or after bowel surgery.
- Gastro-intestinal surgery – use with caution after recent GI surgery as opioids may alter GI motility.
- Gall bladder disease or gall stones – opioids may cause biliary contraction. Avoid in biliary disorders.
- Hepatic impairment – avoid if severe. Codeine may precipitate coma
- Renal impairment
- Urinary tract surgery – following recent surgery patients will be more prone to urinary retention caused directly by spasm of the urethral sphincter, and via constipation caused by codeine
- Prostatic hypertrophy
- Elderly patients may metabolise and eliminate opioid analgesics more slowly than younger patients
- 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

Excipients

- Codeine Phosphate Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- This medicinal product contains less than 1 mmol sodium (23 mg) per maximum daily dose, that is to say essentially 'sodium- free.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant combinations not recommended

MAOIs (e.g. linezolid, moclobemide, selegiline) due to the possible risk of excitation or depression – avoid concomitant use and for 2 weeks after discontinuation of MAOI.

Combinations to be used with caution

Respiratory related

Sedative medicines such as benzodiazepines or related drugs - the concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

Alcohol enhanced sedative and hypotensive effect, increased risk of respiratory depression Sedative antihistamines – enhanced sedative and hypotensive effect and increased risk of respiratory depression

- Hypnotics and anxiolytics – enhanced sedative effect, increased risk of respiratory depression

Gastrointestinal related

- Anticholinergics (e.g. atropine) – risk of severe constipation which may lead to paralytic ileus and/or urinary retention
- Metoclopramide and domperidone – antagonise effect on GI activity
- Antidiarrhoeal drugs (e.g. loperamide, kaolin) – increased risk of severe constipation. CNS related
- Anaesthetics – enhanced sedative and hypotensive effect.

  Tricyclic antidepressants – enhanced sedative effect.

- Antipsychotics – enhanced sedative and hypotensive effect.
- Opioid antagonists e.g. buprenorphine, naltrexone, naloxone – may precipitate withdrawal symptoms.
- Quinidine – reduced analgesic effect.
- Antihypertenstive drugs – enhanced hypotensive effect.
- Pharmacokinetic interactions.
- Ciprofloxacin – avoid premedication with opioids as they reduce plasma ciprofloxacin concentration.
- Ritonavir may increase plasma levels of opioid analgesics such as codeine.
- Mexiletine – delayed absorption of mexiletine.
- Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

During labour opioids enter the foetal circulation and may cause respiratory depression in the neonate. Respiratory malformation in neonates may be associated with exposure to codeine during pregnancy. Gastric stasis and a risk of inhalation pneumonia could occur in the mother during labour. Administration should be avoided during the late stages of labour and during the delivery of a premature infant.

Breast-feeding

Codeine is contraindicated in women during breast-feeding

Administration to nursing women is not recommended as codeine phosphate may be secreted in breast milk and may cause respiratory depression in the infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Opioid toxicity

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 machine

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Effects such as confusion, drowsiness, dizziness, hallucinations, blurred or double vision or convulsions may occur. The effects of alcohol are enhanced with this combination. Driving and operating machinery is not recommended if affected

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

The medicine is likely to affect your ability to drive

4.8 Undesirable effects

Immune system disorders: (may be caused by histamine release) – including rash, urticaria, pruritus, difficulty breathing, increased sweating, redness or flushed face.

Psychiatric disorders: frequency unknown: drug dependence.

Nervous system disorders: confusion, drowsiness, malaise, tiredness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental depression, headache or nightmare, raised intracranial pressure, tolerance or dependence, dysphoria, hypothermia.

Eye disorders: - miosis, blurred or double vision.

Cardiac disorders: bradycardia, palpitations, hypotension, orthostatic hypotension, tachycardia.

Respiratory, thoracic and mediastinal disorders: respiratory depression with larger doses.

Gastrointestinal disorders: constipation (too constipating for long-term use), biliary spasm, nausea, vomiting, dry mouth.

Muscoskeletal, connective tissue and bone density: muscle rigidity.

Renal and urinary disorders: ureteral spasm, antidiuretic effect, urinary retention.

Reproductive system and breast disorders: decrease in libido and potency.

General disorders and administration site conditions: uncommon: drug withdrawal syndrome. Withdrawal effects: abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration, and increase in heart rate, respiratory rate and blood pressure.

NOTE – tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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

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

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

5. Pharmacological properties

5.1 Pharmacodynamics 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.

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

5.2 Pharmacokinetic properties

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

Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Micro Crystalline Cellulose pH -102, Sodium Starch Glycolate, Sodium Methyl Paraben, Sodium Propyl Paraben, Talcum Powder, Magnesium Stearate, Colloidal Silicon dioxide

6.2 Incompatibilities

None stated

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature below 30°C, protect from light and moisture.

6.5 Nature and contents of container

VERCOD (Codeine Phosphate Tablets BP 30 mg) PACK

SIZE:

10x10x10

Primary Packing –

i) Aluminum foil printed for blister 158 mm. ii)

PVC Light Amber 160mm

SECONDARY PACKAGING: Printed Carton

1. 10 tablets are packed in amber colour Alu/PVC Blister pack.
2. 10 Such PVC Blister packs are packed in inner carton.
3. 10 such inner cartons are packed in a printed outer carton.

These container closure systems are suitable for storage, efficacy, transportation and use of the Finished product

6.6 Special precautions for disposal and other handling

None

7. Registrant

Generics Africa Limited

Aqua Office Suites, 5th Floor, Murang'a Road, Nairobi, Kenya

+254 20 2010103 www.Genericsafrica.com

8. Manufacturer

Verve Human Care Laboratories

15-A, Pharmacity, Selaqui,

Dehradun-248011

India

9. Date of revision of the text

Not applicable

10. Dosimetry (If Applicable)

Not applicable

11. Instructions for preparations of Radiopharmaceuticals (if Applicable) Not applicable

1.4.2. Container Labelling

A. Outer Carton

- Proprietary Name : VERCOD

- International Non-Proprietary name(s) of the Active Pharmaceutical Ingredient(s): Codeine Phosphate
- Amount of each Active Pharmaceutical Ingredient present in a dosage unit: 30 mg
- List of excipients: Micro Crystalline Cellulose, Sodium Starch Glycolate, Sodium Methyl Paraben, Sodium Propyl Paraben, Talcum Powder, Magnesium Stearate, Colloidal Anhydrous Silica, P.V.P.k-30, Purified water, Colloidal Anhydrous Silica.
- Pharmaceutical form and contents of the container: Uncoated Tablets & ALU/PVC
- Method and route(s) of administration and the statement "Read the patient information leaflet before use."
- Special warning that the medicinal product must be stored out of the reach and sight of children ("Keep out of the reach and sight of children.").
- Other special warnings and handling precautions, if necessary (e.g. in case of specific toxicity of the agents.)
- The word "sterile" if the product is sterile. NA
- Batch number assigned by the manufacturer. NA
- The manufacturing date. NA
- The expiry date. NA
- Special storage conditions, if applicable. NA
- Special precautions for disposal of unused medicinal products or waste material derived from such medicinal products, if appropriate. NA
- The name and address of the Marketing Authorization Holder.
  Verve Human Care Laboratories
  15-A, Pharmacity,
  Selaqui, Dehradun-248011 India

- Physical address of the site responsible for release of the finished product.

  Verve Human Care Laboratories
  15-A, Pharmacity,
  Selaqui, Dehradun-248011 India

- Advice on general classification for distribution, e.g., Controlled Medicines, Prescription Only Medicines, Pharmacy Only Medicines, Over-the-Counter and General Sales List. : Controlled Medicines Instruction on use.
- The proprietary name, strength and expiry date in braille (Marburg Medium.) The registration number issued by Rwanda FDA.

B. Blisters and strips

- Name, strength and pharmaceutical form of the FP.
  Name: VERCOD (Codeine Phosphate Tablets BP 30 mg)
  Pharmaceutical form: Uncoated tablets
  Strength: 30 mg
- Name and physical address of the manufacturing site (the site responsible for release of the finished product.)

  Verve Human Care Laboratories
  15-A, Pharmacity,
  Selaqui, Dehradun-248011 India
- The batch number assigned by the manufacturer.: NA
- The expiry date [Note that for co-blistered products, the expiry date is that of the product which expires first.] NA
- The manufacturing date, if space is enough. NA
- The batch number assigned by the manufacturer. NA
- Directions for use, and any warnings or precautions that may be necessary.

1.4.3. Patient Information Leaflet

Not Applicable as this Product is subjected to medical prescription:

- Controlled Drug Substance
- Prescription Only Medicine, POM