# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Co-codamol 15 mg/500 mg Capsules.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 15 mg of codeine phosphate hemihydrate and 500 mg of paracetamol.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule.

Hard gelatin capsule of size 0EL, with a pearl red opaque cap and white opaque body, both imprinted with “15/500”.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the relief of moderate pain.

Indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with codeine in order to minimize the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

*Adults*

Two capsules not more frequently than every 4 to 6 hours, up to a maximum of 8 capsules in 24 hours.

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

*Pediatric population*
*Adolescents aged 16 to 18 years*
One to two capsules every 6 hours when necessary up to a maximum of 8 capsules in 24 hours.

*Children and adolescents aged 12 to 15 years*
One capsule every 6 hours when necessary to a maximum of 4 capsules in 24 hours.

Duration of treatment

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

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

*Children under 12 years*
Not recommended for children under 12 years of age. This is because of codeine risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of administration

For oral administration

Treatment goals and discontinuation

Before initiating treatment with Co-codamol 15 mg/500 mg Capsules, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In

absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

## 4.3 Contraindications

Hypersensitivity to paracetamol or codeine which is rare.

Hypersensitivity to any of the other constituents.

Conditions where morphine and opioids are contraindicated e.g.

- Acute asthma
- Respiratory depression
- Acute alcoholism
- Head injuries
- Raised intracranial pressure
- Following biliary tract surgery
- Breast-feeding (see section 4.6)

Monoamine oxidase inhibitor therapy, concurrent or within 14 days.

In all pediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

Not recommended for children under 12 years of age.

In patients for whom it is known that they are CYP2D6 ultra-rapid metabolizers (see section 4.4).

## 4.4 Special warnings and precautions for use

**Tolerance and opioid use disorder (abuse and dependence)**

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Co-codamol 15 mg/500 mg Capsules. Repeated use of Co-codamol 15 mg/500 mg Capsules can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Co-codamol 15 mg/500 mg Capsules may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Co-codamol 15 mg/500 mg Capsules and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.
Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained online, 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.
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.

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.
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 new-born infants will experience neonatal withdrawal syndrome.

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

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.

Hepatobiliary disorders

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

CYP2D6 metabolism

Codeine is partially metabolized 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 metabolizer 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 nausea, vomiting, constipation, lack of appetite, somnolence, shallow breathing, small pupils and confusion. 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 metabolizers in different populations are summarized below:

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

The leaflet will describe in the “pregnancy and breast-feeding” subsection of section 2 that Co-codamol is contraindicated in breast-feeding.

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.

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

Concomitant use of Co-codamol 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 Co-codamol 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 (see section 4.5).

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

Risks from concomitant use of opioids and alcohol

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see section 4.5).

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, hypothyroidism and those with inflammatory or obstructive bowel disorders, Addison's disease or

myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.
Co-codamol should be used upon medical advice in patients with

- Severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.
Patients should be advised to consult a doctor should symptoms persist and to keep the product out of the reach and sight of children.
Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).
The risk-benefit of continued use should be assessed regularly by the prescriber.

The leaflet will describe similar statements in prominent positions in section 2:

Do not take for longer than directed by your prescriber.

Taking codeine regularly for a long time can lead to addiction.

Taking a pain killer 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.

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

<u>Co-codamol 15 mg/500 mg Capsules contain sodium</u>

Co-codamol contains less than 1 mmol sodium (23 mg) per capsule, that is to say it is essentially 'sodium free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

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 (see section 4.4).

Concomitant use of Co-codamol 15 mg/500 mg Capsules with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Alcohol and opioids

The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

CYP2D6 inhibitors

Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine.

Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers

Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and rifampicin should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Flucloxacillin

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Regular codeine use during pregnancy may cause drug dependence in the fetus, 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.

Breast-feeding

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

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant.

Codeine should not be used during breast-feeding (see section 4.3). Co-codamol 8 mg/500 mg tablets are contraindicated during breast-feeding.

Fertility

There are no data on the effects of Co-codamol 8 mg/500 mg tablets on human fertility.

Fertility was unaffected following paracetamol and codeine treatment in animal studies (see section 5.3).

## 4.7 Effects on ability to drive and use machines

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

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

## 4.8 Undesirable effects

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Tolerance and dependence can occur, especially with prolonged high dosage of codeine.

- 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

Adverse effects of paracetamol are rare:
<u>Blood and lymphatic system disorders</u>

Very rare: thrombocytopenia, neutropenia, leucopenia.

Not known: agranulocytosis.

<u>Immune system disorders</u>

Hypersensitivity including skin rash may occur.

Not known: Anaphylactic shock, angioedema.

Psychiatric disorders

Frequency unknown: drug dependence (see section 4.4).

Vascular disorders

Not known: hypotension (with high doses).

Respiratory, thoracic and mediastinal disorders

Not known: bronchospasm (see section 4.4).

Skin and subcutaneous disorders

Very rare cases of serious skin reactions have been reported.

General disorders and administration site conditions

Uncommon: drug withdrawal syndrome.

Very rare occurrence of pancreatitis.

Metabolism and nutrition disorders

Not known: High anion gap metabolic acidosis.

Hepatobiliary disorders

Not known: Sphincter of Oddi dysfunction.

Drug dependence

Repeated use of Co-codamol 15 mg/500 mg Capsules can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

**Description of selected adverse reactions**

High anion gap metabolic acidosis

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

in these patients.

Reporting of suspected adverse reactions

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

## 4.9 Overdose

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 help if they occur.

Codeine

The effects of codeine over dosage 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**

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 present within one hour of ingestion of more than 350 mg or a child more than 5 mg/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.

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

**Risk factors**

If the patient,

a. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes, or

b. Regularly consumes ethanol in excess of recommended amounts, or

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

**Symptoms**

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

**Management**

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

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations

ATC Code: N02B E51

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

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

## 5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and undergoes extensive biotransformation. The major metabolites are inactive phenolic sulphate and glucuronide conjugates. An adequate supply of SH groups can prevent hepatic toxicity. Paracetamol is excreted in the urine. The elimination half-life varies from about 1 to 4 hours.

Codeine is absorbed from the gastrointestinal tract and peak plasma concentrations are produced in about 1 hour. It is metabolised in the liver to morphine and norcodeines. Codeine and its metabolites are excreted almost entirely by the kidney. The plasma half-life is between 3 and 4 hours.

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

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

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

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

## 5.3 Preclinical safety data

Paracetamol

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Capsule content

maize starch

sodium starch glycolate (Type A)

povidone (K-30)

magnesium stearate

Capsule shell

mica based titanium dioxide

iron oxide red

gelatin

sodium laurilsulfate

Printing ink

shellac

black iron oxide

trace amount (less than 1 ppb) of potassium salts of potassium hydroxides

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

36 months.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Alu-PVC/PVDC blister pack of 100 capsules.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Key Pharmaceuticals Ltd.

Galen House, 83 High Street, Somersham,

Cambridgeshire, PE28 3JB, UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 34424/0073

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2023

## 10 DATE OF REVISION OF THE TEXT

13/03/2026