Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Migraleve Yellow Film-coated Tablets Paracetamol 500mg Codeine phosphate 8mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Migraleve Yellow tablet contains:
Paracetamol 500 mg (as Paracetamol DC 96%).
Codeine phosphate 8 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet. (Tablet)
Yellow film-coated capsule-shaped tablets engraved 'MGE' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prevention and treatment of migraine attacks which can include the symptoms of migraine headache, nausea and vomiting. Route of administration: oral.

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

4.2 Posology and method of administration

Do not take for more than 3 days continuously without medical review. If prescribed do not take for longer than directed.

Codeine-containing products should be used at the lowest effective dose for the shortest period of time.

Adults and the elderly: One to two Migraleve Pink tablets to be swallowed immediately it is known that a migraine attack has started or is imminent. If further treatment is required, one to two Migraleve Yellow tablets every 4-6 hours.

Maximum dose: 8 tablets (two Migraleve Pink and six Migraleve Yellow) in 24 hours.

Paediatric population:

Children aged 16 - 18 years: One to two Migraleve Pink tablets to be swallowed immediately it is known that a migraine attack has started or is imminent. If further treatment is required, one to two Migraleve Yellow tablets every 6 hours.

Maximum dose: 8 tablets (two Migraleve Pink and six Migraleve Yellow) in 24 hours.

Children 12 - 15 years: One Migraleve Pink tablet to be swallowed immediately it is known that a migraine attack has started or is imminent. If further treatment is required, one Migraleve Yellow tablet every 6 hours.

Maximum dose: 4 tablets (one Migraleve Pink and three Migraleve Yellow) in 24 hours.

Children aged below 12 years:
Do not give to children under 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see Section 4.3 and Section 4.4).

Paracetamol Warnings:
Renal impairment:
It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:
In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged.

The daily dose should not exceed 2g/day unless directed by a physician.

The Elderly:
Experience has indicated that normal adult dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

The maximum daily dose should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

4.3 Contraindications

Hypersensitivity to the active substances (Paracetamol and / or Codeine phosphate) or to any of the excipients listed in section 6.1.

Codeine-containing products are contraindicated for postoperative pain management in all paediatric patients (0-18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see Section 4.4).

In women during breastfeeding (see Section 4.6).

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

Migraleve tablets are contraindicated for children below 12 years of age.

4.4 Special warnings and precautions for use

Migraine should be medically diagnosed. Because some medicines do not combine, patients should be advised to tell their doctor if they are already taking prescribed medicines. They should also be advised to consult their doctor if symptoms persist. Migraleve tablets are intended for short-term use only. Migraleve tablets contain potent medicaments and should not be taken continuously for extended periods without the advice of a doctor.

Do not exceed the stated dose.

Codeine

Codeine is an opioid agent. Tolerance, psychological and/or physical dependence may occur with prolonged use and/or high doses of codeine (see Section 4.8). Prolonged regular use for more than 3 days, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. Opioid-induced hyperalgesia has been reported with longer term treatment or withdrawal from opioids, particularly at high doses.

Codeine should be used with caution in patients with convulsive disorders, head injuries, and in conditions in which intracranial pressure is raised.

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma and death (see Section 4.5).

Codeine should be used with caution in patients with decreased respiratory reserve, such as bronchial asthma, pulmonary oedema, obstructive airways disease, acute respiratory depression or sleep-related breathing disorders such as sleep apnoea syndromes (obstructive and central).

Codeine should be used with caution in patients with obstructive bowel disorders and in patients at risk of paralytic ileus.

Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients (see section 4.8).

Codeine should be used with caution in patients with renal or hepatic impairment.

Opioids have also been associated with:

- Serotonin syndrome resulting from concomitant administration of serotonergic drugs e.g., certain antidepressants, anti-anxiety, other psychiatric or migraine medications (see Section 4.5).
- Adrenal insufficiency.
- Androgen deficiency.

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

Even at therapeutic dosage regimens, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience signs of overdose such as extreme sleepiness, confusion, or shallow breathing (see Section 4.9). Other general symptoms of opioid toxicity include small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory 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%

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose (see Section 4.9).

Use of the drug should be discontinued and immediate medical advice sought at the earliest sign of codeine toxicity including symptoms such as confusion, shallow breathing or extreme sleepiness which may be life threatening.

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.

Paracetamol

Paracetamol should be administered with caution under the following circumstances (see section 4.2):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol-containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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 patient 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.

4.5 Interaction with other medicinal products and other forms of interaction

Codeine

Concomitant use with central nervous system depressants (e.g. barbiturates, chloral hydrate, benzodiazepines, phenothiazines, alcohol and centrally acting muscle relaxants) may cause additive CNS depression and respiratory depression.

Concurrent use with other opioid receptor agonists may cause additive CNS depression, respiratory depression and hypotensive effects.

Codeine analgesia is believed to be dependent upon the cytochrome P450 isoenzyme CYP2D6 catalysed o-demethylation to form the active metabolite morphine although other mechanisms have been cited. An interaction with quinidine, methadone and paroxetine (CYP2D6 inhibitors) leading to decreased plasma concentrations of morphine has been described, which may have the potential to decrease codeine analgesia.

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol) and monoamine oxidase (MAO) inhibitors may result in serotonin syndrome.

Paracetamol

The use of drugs which induce hepatic microsomal enzymes, such as anticonvulsants and oral contraceptive steroids, may increase the extent of metabolism of paracetamol, resulting in reduced plasma concentrations of the drug and a faster elimination rate.

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

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.

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.
High anion gap metabolic acidosis from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of paracetamol and flucloxacillin. Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs. Consumers should be instructed to ask their health care provider before use if they are taking the antibiotic 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

This product should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus.

Codeine crosses the placenta. Neonates who have been exposed to codeine in utero can develop withdrawal syndrome (neonatal abstinence syndrome) after delivery. Cerebral infarction has been reported in this setting.

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

When given to the mother in labelled doses, paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is effectively metabolised by foetal sulfate conjugation.

Breastfeeding

Codeine is contraindicated in breastfeeding women (see Section 4.3).

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

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.

Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose).

4.7 Effects on ability to drive and use machines

May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink.

4.8 Undesirable effects

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

Prolonged use of a painkiller for headaches can make them worse.

Very rare cases of serious skin reactions have been reported with paracetamol.

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with paracetamol, codeine, or the combination of paracetamol/codeine are listed below by System Organ Class (SOC).

The frequencies are defined according to the following convention:
Very common (≥1/10);
Common (≥1/100 and <1/10);
Uncommon (≥1/1,000 and <1/100);
Rare (≥1/10,000 and <1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence is unavailable, frequency category is listed as 'Not known'.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Blood and lymphatic system disorders	Not known	Blood disorder (including thrombocytopenia and agranulocytosis)[4]
Immune system disorders	Not known	Anaphylactic reaction[3]
	Rare	Hypersensitivity [2, 3]
Psychiatric disorders	Uncommon	Euphoric mood[5]
	Not known	Agitation[5]
	Not known	Drug dependence[2]
	Not known	Drug withdrawal syndrome[2]

Nervous system disorders	Very common	Somnolence[1,2]
	Common	Dizziness[1, 5]
	Common	Headache[5]
Vascular disorders	Uncommon	Flushing[5]
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm[2]
	Not known	Dyspnoea[5]
	Not known	Respiratory depression[2]
Gastrointestinal disorders	Very common	Nausea[1,2]
	Common	Constipation[1,2]
	Common	Dry mouth[1]
	Common	Vomiting[1,2]
	Uncommon	Abdominal pain[5]
	Uncommon	Dyspepsia[2]
	Not known	Pancreatitisacute (particularly in patients with a history of cholecystectomy[2]
Hepatobiliary disorders	Not known	Liver injury[3]
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis[1]
	Uncommon	Pruritus[3,5]
	Uncommon	Rash[3]
	Uncommon	Urticaria[2,3]
	Not known	Angioedema[5]
	Not known	Dermatitis[2]
	Not known	Fixed eruption[3]
Renal and urinary disorders	Uncommon	Nephropathy toxic[3]
Investigations	Not known	Transaminases increased[6]
Metabolism and nutritiondisorders	Not known	High anion gap metabolic acidosis

[1] *Adverse events reported by ≥1% of codeine/paracetamol treated subjects in 27 randomised placebo-controlled trials*
[2] *Associated with codeine*
[3] *Associated with paracetamol*
[4] *Reported following paracetamol use, but not necessarily causally related to the drug*
[5] *Associated with paracetamol / codeine combination*
[6] *Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.*

Other adverse drug reactions (codeine class effects) include:

- *Sedation*
- *Vertigo*
- *Bronchospasm*
- *Gastrointestinal disorder, such as dyspepsia, nausea, vomiting, constipation*
- *Euphoric mood*
- *Drug dependence can develop following long-term use of high doses*

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 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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Paracetamol

Paracetamol overdose can result in liver damage which may be fatal. Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.
Risk factors include:

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.
Cardiac arrhythmias and pancreatitis have also been reported.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

Emergency Procedure:
Immediate transfer to hospital.
Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour. The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.
Symptomatic treatment should be implemented.

Codeine

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

Codeine overdose associated with 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. Other risks of codeine overdose include cardio-respiratory arrest, brain oedema, coma, confusional state, seizure, hypoxia, ileus, renal failure, respiratory failure and stupor.

Management of codeine overdose includes 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 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 four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, codeine and paracetamol
ATC code: N02AJ06

Paracetamol has analgesic, antipyretic and mild, acute anti-inflammatory properties. Paracetamol inhibits prostaglandin synthesis, especially in the CNS.Paracetamol does not inhibit chronic inflammatory reactions.

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.

Codeine also has anti-tussive properties.

5.2 Pharmacokinetic properties

Paracetamol is rapidly absorbed from the upper G.I. tract after oral administration, with the small intestine being an important site of absorption. Peak blood levels of 15-20 mcg/ml after normal 1 g oral doses of paracetamol occur within 30 – 90 minutes. Depending upon dosage form, it is rapidly distributed throughout the body and is primarily metabolised in the liver with excretion via the kidney. Elimination half-life is about 2 hours after reaching a peak following a 1 g oral dose. Paracetamol crosses the placental barrier and is present in breast milk.

Codeine is absorbed from the gastro-intestinal tract and peak plasma concentrations occur after one hour. Codeine is metabolised by O- and N- demethylation in the liver to morphine, norcodeine and other metabolites. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Codeine is not extensively bound to plasma proteins. The plasma half-life has been reported to be between 3 and 4 hours.

5.3 Preclinical safety data

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

Gelatin
Magnesium stearate
Colloidal anhydrous silica
Stearic acid
Pregelatinised maize starch

Opadry yellow OY-6126*

*Opadry Yellow OY-6126 contains:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Yellow iron oxide (E172)
Quinoline yellow aluminium lake (E104) consisting of quinoline yellow (E104) and aluminium oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Clear amber PVC/Aluminium foil blisters.

Or

Clear amber PVC/Laminated paper and aluminium foil child resistant blisters.

Packs of 12, 24 and 48 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

JNTL Consumer Health I (Ireland) Limited
Office 5, 6 And 7
Block 5
High Street
Tallaght
Dublin 24
D24 YK8N
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23490/014/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

February 2025