SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Migraleve

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Migraleve Pink tablet contains:	
Paracetamol DC 96% (equivalent to Paracetamol 500 mg)	520 mg
Codeine Phosphate	8 mg
Buclizine Hydrochloride	6.25 mg

Each Migraleve Yellow tablet contains:	
Paracetamol DC 96% (equivalent to Paracetamol 500 mg)	520 mg
Codeine Phosphate	8 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets.

Migraleve Pink Tablets
Pink, capsule-shaped, film-coated tablets marked MGE on one face.

Migraleve Yellow Tablets
Yellow, capsule-shaped, film-coated tablets marked MGE on one face.

4.1 Therapeutic Indications

For the short-term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone such as migraine attacks including the symptoms of migraine headache, nausea and vomiting.

Codeine is indicated in children 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

Route of administration – oral.

POM only
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 minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

P only

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.

POM and P

Adults and Children 16 years and over: 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, two Migraleve Yellow tablets every 4 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 4 hours.

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

Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

4.3 Contraindications

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

In all paediatric patients (0 to 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).

Head injury; in conditions in which intracranial pressure is increased; acute respiratory depression; obstructive bowel disorders and in patients at risk of paralytic ileus.

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.

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.

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). Codeine may cause addiction if taken continuously for more than three days.

POM only
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 (e.g., major depression).

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.

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.

POM and P

Codeine should be used with caution in patients with convulsive disorders, decreased respiratory reserve, such as bronchial asthma, pulmonary oedema and obstructive airways disease.

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).

Administration of pethidine and possibly other opioids analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. If the use of codeine is considered essential then great care should be taken in patients taking MAOIs or within 14 days of stopping MAOIs (see section 4.5).

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

If codeine is taken for headaches for more than 3 days it can make them worse (medication overuse headaches).

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

Opioids have also been associated with:

- Adrenal insufficiency (long term use).
- Hypogonadism.
- Prostatic hypertrophy and urethral stenosis (in adults).

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.

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%-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.

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

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Chronic alcohol users should ask their doctors whether they should take paracetamol or other pain relievers or fever reducers.

Do not take anything else containing paracetamol while taking this medicine.

Taking this product with other paracetamol-containing products, could lead to overdose and should therefore be avoided.

Patients should be informed about the signs of serious skin reactions, and the 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 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.

Buclizine

Buclizine is a sedating antihistamine that may enhance the sedative effects of central nervous system depressants, including alcohol, sedatives, tranquilizers, tricyclic antidepressants, MAOIs and antimuscarinics drugs. While taking this product, patients should be advised to avoid alcoholic beverages and consult a

healthcare professional prior to taking with central nervous system depressants (see Section 4.5).

Buclizine has an antimuscarinic action and therefore should be used with caution in prostatic hypertrophy and urinary retention. Also where susceptibility exists to angle-closure glaucoma.

For POM (Prescription Only Medicine) Pack:

The label will state (To be displayed prominently on the 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.

Front of Pack
Can cause addiction
Contains opioid

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

- This medicine contains paracetamol. Do not take anything else containing paracetamol while taking this medicine.
-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.

For P (Pharmacy only) Pack:

The label will state:

Front of pack

- Can cause addiction.
- Contains opioid.
- For three days use only.

Back of Pack

- List of indications as agreed in 4.1 of the SmPC.
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

4.5 Interactions with other medicinal products and other forms of interactions

Codeine

Codeine may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility.

Concomitant use with central nervous system depressants [e.g. alcohol, barbiturates, chloral hydrate, benzodiazepines, anti-psychotics (including phenothiazines), general anaesthetics 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 should be given with care to patients receiving monoamine oxidase inhibitors (MAOIs) or who have used MAOIs in the previous two weeks. MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Paracetamol

Drugs which induce hepatic microsomal enzymes

Metabolism of paracetamol possibly accelerated by carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone (also isolated reports of hepatotoxicity).

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.

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).

Buclizine

Sedating antihistamines, such as buclizine, have an additive sedative effect with alcohol and other CNS depressants. Sedating antihistamines have an additive

antimuscarinic action with other antimuscarinic drugs such atropine and some antidepressants (both tricyclics and MAOIs).

4.6 Fertility, pregnancy and lactation

Pregnancy

POM only
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.

P only
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.

POM and P
There is inadequate evidence for the safety of codeine in human pregnancy. 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. Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

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 if clinically needed 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 therapeutic doses (1 g single dose), paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is metabolised in the foetus by conjugation with sulfate and increasingly with glutathione.

Clinical data with use of buclizine in humans are not adequate to establish safety during pregnancy. Although experiments in some animal species gave rise to adverse effects following the administration of buclizine to pregnant animals e.g. foetal abnormalities and maternal deaths, these occurred at doses in excess of 120 times the human daily dose.

Breast-feeding

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant (see section 4.3).

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.

Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose). Available published data do not contraindicate breast-feeding.

There are no data available relating to the safety of buclizine in breast-feeding mothers.

4.7 Effects on Ability to Drive and Use Machines

May cause drowsiness. If affected do not operate machinery.

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 taking 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 defence') if:
    - The medicine has been taken to treat a medical or dental problem and
    - You have taken it according to the information provided with the medicine and
    - It was not affecting your ability to drive safely.

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law.

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, buclizine hydrochloride, or the combinations of paracetamol/codeine or paracetamol/codeine/buclizine hydrochloride 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	*Very rare*	*Anaphylactic reaction*[3] *(including skin rash)*
	Very rare	*Hypersensitivity*[2,3,5]
Psychiatric disorders	*Uncommon*	*Euphoric mood*[6]
	Not known	*Drug dependence*[2] *(see section 4.4)*
Nervous system disorders	*Very common*	*Headache*[5,6]
	Very Common	*Somnolence*[1,2,5]
	Common	*Dizziness*[1,2,5,6]
	Not known	*Psychomotor skills impaired*[5]
Eye disorders	*Not known*	*Vision blurred*[5]
Vascular disorders	*Very common*	*Flushing*[6]
Respiratory, thoracic and mediastinal disorders	*Not known*	*Bronchospasm*[2]
	Not known	*Dyspnoea*[6]

	Not known	*Increased viscosity of bronchial secretion*[5]
	Not known	*Respiratory depression*[2]
Gastrointestinal disorders	*Very common*	*Nausea*[1,2]
	Common	*Constipation*[1,2]
	Common	*Dry mouth*[1,2,5]
	Common	*Vomiting*[1,2]
	Not known	*Abdominal pain*[6]
	Not known	*Dyspepsia*[2]
	Not known	*Gastrointestinal disorder*[5]
	Not known	*Pancreatitis acute*[2] *(in patients with a history of cholecystectomy)*
Hepatobiliary disorders	*Not known*	*Liver injury*[3,8]
Skin and subcutaneous tissue disorders	*Common*	*Hyperhidrosis*[1,2]
	Uncommon	*Rash*[3,5]
	Not known	*Angioedema*[5,6]
	Not known	*Dermatitis*[2]
	Not known	*Erythema*[5]
	Not known	*Fixed eruption*[3]
	Not known	*Pruritus*[2,6]
	Not known	*Urticaria*[2,3,5]
Renal and urinary disorders	*Not known*	*Dysuria*[2,5]
	Not known	*Nephropathy toxic*[3]
General disorders and administration site conditions	*Uncommon*	*Drug withdrawal syndrome*[2]
Investigations	*Not known*	*Transaminases increased*[7]
Metabolism and nutrition disorders	*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 buclizine*
[6]*Associated with paracetamol / codeine combination*
[7]*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.*
[8]*Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year.*

Other known ADRs that occur with codeine include: anorexia, antidiuretic effect, hypothermia, malaise, muscle fasciculation, and seizures.

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
- Adrenal insufficiency (long term use)
- Hypogonadism

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 the 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

Codeine

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 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 cardiorespiratory arrest, 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.

Paracetamol

Liver damage is possible in adults and adolescents (≥12 years of age) who have taken 7.5g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:

If the patient

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

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms

Symptoms of paracetamol overdose in the first 24 hours are pallor, hyperhidrosis, malaise, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis.

Abnormalities of glucose metabolism and metabolic acidosis may occur. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased. These clinical events associated with paracetamol overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, 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 and pancreatitis have 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.

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 NPIS or a liver unit.

Buclizine

Overdose with sedating antihistamines is associated with antimuscarinic, extrapyramidal, and CNS effects. When CNS stimulation predominates over CNS depression, which is more likely in children or the elderly, it causes ataxia, excitement, tremors, psychoses, hallucinations and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, CNS depression is more common with drowsiness, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, codeine and other non-opioid analgesics
ATC code: N02AJ09

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.

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.

The combination of paracetamol and codeine has been shown to have hyperadditive analgesic effects in animals.

Buclizine is a piperazine derivative with the actions and uses of H_1-receptor antagonists. It has anti-muscarinic and central sedative properties. It is used mainly for its anti-emetic properties.

5.2. Pharmacokinetic Properties

Paracetamol is rapidly absorbed from the upper GI tract after oral administration, with the small intestine being an important site of absorption. Peak blood levels of 15-20mcg/ml after normal 1g 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 1g 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.

Buclizine hydrochloride is more slowly absorbed from the GI tract (Tmax 3 hours). The elimination half-life is approximately 15 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

Migraleve Pink Tablets
Gelatin
Magnesium Stearate
Colloidal Anhydrous Silica
Stearic Acid
Pregelatinised Maize Starch
Erythrosine (E127)
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Aluminium Oxide

Migraleve Yellow Tablets
Gelatin
Magnesium Stearate
Colloidal Anhydrous Silica
Stearic Acid
Pregelatinised Maize Starch
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Iron Oxide Yellow (E172)
Quinoline Yellow (E104)
Aluminium Oxide

6.2. Incompatibilities

None known.

6.3 Shelf life

3 years

6.4. Special precautions for storage

None

6.5 Nature and contents of container

Packs of: 12 tablets (8 Migraleve Pink and 4 Migraleve Yellow)
Packs of: 24 tablets (16 Migraleve Pink and 8 Migraleve Yellow)
Packs of: 48 tablets (32 Migraleve Pink and 16 Migraleve Yellow)

Blister strips consist of clear amber PVC blister film and paper/aluminium foil child-resistant blister lidding.

6.6 Special precautions for disposal and handling

No special precautions for disposal.

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
50 – 100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8. MARKETING AUTHORISATION NUMBER

PL 15513/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2009

10 DATE OF REVISION OF THE TEXT

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