SUMMARY OF PRODUCT CHARACTERISTICS

MUSCOL®

Tablets

1. NAME OF THE MEDICINE

Muscol Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Orphenadrine citrate 30 mg and paracetamol 500 mg.

For the full list of excipients, see Section 6.1 - "List of excipients".

3. PHARMACEUTICAL FORM

Tablets.

Light pink, round flat tablet with beveled edges, scored in half on one side and engraved "IKA" on the other side.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Relief of mild to moderate pain of acute musculoskeletal disorders.

4.2. Dose and method of administration

Adults
2 tablets, three times daily.

4.3. Contraindications

- Hypersensitivity to the active substances (paracetamol or orphenadrine citrate) or to any of the expients listed in section 6.1 - "List of excipients".
- Glaucoma
- Prostatic hypertrophy or obstruction at the bladder neck,
- Myasthenia gravis
- Oesophageal spasm and pyloric or duodenal obstruction.

4.4. Special warnings and precautions for use

Identified precautions

Concomitant treatment with other medicines that contain orphenadrine or paracetamol is not recommended.

Orphenadrine citrate
Safety of continuous long-term therapy with orphenadrine has not been established. Therefore, if orphenadrine is prescribed for prolonged use, periodic monitoring of blood, urine and liver function is recommended.

Orphenadrine citrate should be used with caution in patients with tachycardia, cardiac decompensation, coronary insufficiency or cardiac arrhythmias, Gilbert's syndrome and Glucose – 6 – phosphate – dehydrogenase deficiency.

Paracetamol
Muscol may be dangerous when used in large amounts or for long. Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. Hepatotoxicity may develop following as little as 10 to 15 g of paracetamol and hepatic failure is known to occur occasionally with long term use of paracetamol.
Paracetamol should be used with caution in patients with hepatic or renal dysfunction.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Caution is advised in patients with known analgesic intolerance or known bronchial asthma as hypersensitivity reactions including bronchospasm are possible.

Severe cutaneous adverse reactions (SCARs): Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop treatment immediately and seek medical advice.
Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Paracetamol can cause accidental poisoning in toddlers and infants. Paracetamol-containing products should be kept well out of reach of children.

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 and 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.

Use in hepatic impairment
Use with caution in patients with impaired liver function: Underlying liver disease increases the risk of paracetamol-related liver damage.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index, are chronic heavy users of alcohol or have sepsis.

In patients with glutathione depleted states the use of paracetamol may increase the risk of metabolic acidosis.

Use in renal impairment
Use with caution in patients with impaired kidney function. Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates.

Use in the elderly
The elderly should be advised to take a reduced dosage as they may be more susceptible to anti-cholinergic side effects at regular doses.

Paediatric use
Muscol is not recommended for children under 12 years of age.

Effects on laboratory tests
Uric acid and blood glucose: Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interactions with other medicines and other forms of interactions

- Interactions have been reported between orphenadrine and phenothiazines and other drugs with anti-muscarinic properties.
- Concomitant use with alcohol or other CNS depressants should be avoided.
- **Anticoagulants:** Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K medicines. Anticoagulant dosage may require reduction, and patients should be monitored for appropriate coagulation and bleeding complications.
- **Chloramphenicol:** Paracetamol may increase chloramphenicol concentrations by slowing down excretion, entailing the risk of increased toxicity.
- **Cholestyramine:** reduces the absorption of paracetamol if given within 1 hour of paracetamol. Chelating resins can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.
- **Drugs which affect motility:**
  - Paracetamol absorption is increased by medicines that increase gastric emptying, e.g. metoclopramide and domperidone
  - Paracetamol absorption is decreased by medicines that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics.
- **Flucloxacillin:** Co-administration of flucloxacillin with paracetamol may lead to high anion gap metabolic acidosis due to pyroglutamic acidosis, particularly in patients presenting risks factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism (see section 4.4).
- **Probenecid:** Paracetamol excretion may be affected and plasma concentrations altered when given probenecid.
- **Zidovudine:** Paracetamol may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine. Zidovudine may also inhibit the hepatic glucuronidation of paracetamol. When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of Paracetamol and zidovudine should be avoided, because the toxicity of either or both medications may be potentiated.
- **Hepatotoxic Drugs and Liver Microsomal Enzyme Inducers:** The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), alcohol, barbiturates and rifampicin. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

4.6. Fertility, pregnancy and lactation

Effects on fertility
No data available

Use in pregnancy – Pregnancy Category B2
Muscol is not recommended for use during pregnancy.

Use in lactation
Muscol should not be taken during lactation as orphenadrine and paracetamol are excreted into breast milk.

4.7. Effects on ability to drive and use machines

Orphenadrine may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly. Similarly, children should be warned not to participate in activities such as riding a bicycle or playing near traffic.

4.8. Adverse effects (Undesirable effects)

Adverse effects are mainly due to the anti-cholinergic action of orphenadrine and are usually associated with higher doses.

Orphenadrine citrate

More common reactions

The known adverse effects include:

- Dryness of the mouth,
- Tachycardia, palpitation,
- Urinary hesitancy or retention,
- Blurred vision, dilation of the pupils, increased ocular tension,
- Weakness, nausea, headache, dizziness, constipation and drowsiness.

These effects can usually be eliminated by reducing the dose.

Less common reactions

- Sedation,
- Skin rashes and other allergic reactions are very uncommon adverse effects.
- Infrequently an elderly patient may experience some degree of mental confusion.
- Very rare cases of aplastic anaemia associated with the use of orphenadrine have been reported.

Paracetamol

Reports of adverse reactions are rare.

The the following reactions have been reported:

- Dyspepsia
- Sweating
- Erythema
- Urticaria
- Anaphylactic shock
- Angioneurotic oedema
- Difficulty breathing
- Drop in blood pressure
- Nausea
- Allergic reactions such as skin rashes
- Hepatotoxicity (see Section 4.4 – "Special warnings and precautions for use")
- Hypersensitivity reactions.
- Haematological reactions including thrombocytopenia, leukopenia, neutropenia, agranulocytosis and pancytopenia.
- Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP), can be fatal (See section 4.4 - "Special warnings and precautions for use"). Fixed drug eruption and cytolytic hepatitis, which may lead to acute hepatic failure, have also been reported.
- Bronchospasm may be triggered in patients having a tendency of analgesic asthma.
- Not known: Some cases of edema of the larynx, anaphylactic shock, anaemia, bronchospasm, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

- Haemolytic anaemia, particularly in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported. Kounis syndrome has been reported,
- Not known (frequency cannot be estimated from the available data): Metabolism and nutrition disorders - High anion gap metabolic acidosis (HAGMA) [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. Any suspected adverseevents should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9. Overdose

No specific information is available on overdosage with Muscol.

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzymes-inducing drugs are at an increased risk of intoxication, including fatal outcome. Overdosege with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Symptoms and Signs
Orphenadrine overdosage: Known symptoms of overdose with orphenadrine include tachycardia, excitement, confusion and delirium leading to coma. Convulsions, dilated pupils and urinary retention may occur.

Paracetamol overdosage: In adults, hepatotoxicity may occur after ingestion of a single dose of paracetamol 10 to 15 g; a dose of 25 g or more is potentially fatal.

Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop.

Toxic symptoms include vomiting, abdominal pain, hypotension and sweating. Nausea, vomiting, anorexia, pallor and abdominal pain generally appear during the first 24 hours of overdosage with paracetamol. Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage. Overdosage can also lead to pancreatitis, acute renal failure and pancytopenia.

Treatment
Despite lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.
Activated charcoal may reduce absorption of paracetamol if given within one hour after oral ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Where paracetamol intoxication is suspected, intravenous administration of SH group donators such as acetylcysteine may be indicated. Although acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case it is taken for longer.

Further measures will depend on the severity, nature and course of clinical symptoms of intoxication and should follow standard intensive care protocols.

Convulsions and delirium respond to relatively large doses of diazepam, preferably by mouth.
Adequate hydration of the patient is important.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: M03BC51 Orphenadrine, combinations with e.g. paracetamol

Mechanism of action

Orphenadrine is a skeletal muscle relaxant. Paracetamol is an analgesic and antipyretic.

5.2. Pharmacokinetic properties

Orphenadrine

No data available

5.3. Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose, gelatin, sodium starch glycolate, magnesium stearate, purified water, colloidal silicon dioxide, FD&C Red No.3 aluminium lake.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store in a dry place, below 25°C.

6.5. Nature and contents of container

PVC/Aluminium blister pack of 20 or 1000 tablets.

Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. Physicochemical properties

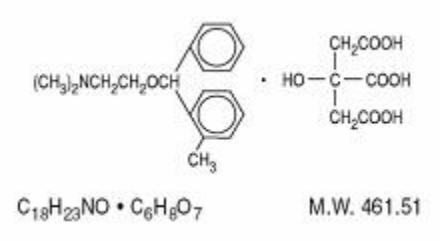
Orphenadrine citrate is white or almost white, crystalline powder. It is sparingly soluble in water, and slightly soluble in alcohol. Paracetamol is a white or almost white, crystalline powder that is sparingly soluble in water and freely soluble in alcohol.

Chemical structure

Orphenadrine citrate

Chemical name: (RS)-N,N-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate

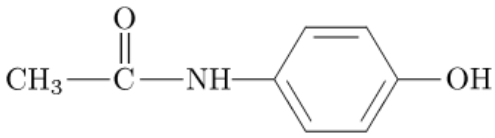
Chemical structure:



Paracetamol

Chemical name: N-(4-Hydroxyphenyl)acetamide

Chemical structure:



CAS number
Orphenadrine citrate: 4682-36-4
Paracetamol: 103-90-2

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Industries Ltd.
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel

8. REGISTRATION NUMBER

018.08.20537

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