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.

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
Orphenadrine citrate should be used with caution in patients with tachycardia, cardiac decompensation, coronary insufficiency or cardiac arrhythmias.

Paracetamol
Paracetamol should be used with caution in patients with hepatic or renal dysfunction.

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.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.

Anyone who develops a skin rash or reaction while using paracetamol should **stop the drug** and seek medical attention right away. 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.

Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

Paracetamol can cause accidental poisoning in toddlers and infants. Paracetamol-containing products should be kept well out of reach of children.
Potentially fatal hepatotoxicity can result from paracetamol overdosage. However, in rare cases, hepatotoxicity has occurred in patients receiving high or excessive doses within therapeutic doses. Certain patients may be more susceptible to paracetamol hepatotoxicity, e.g., chronic alcoholics, patients with liver disease, or those who are malnourished or taking other drugs that induce hepatic enzymes. Because of the risk of hepatotoxicity, patients should be cautioned against the inadvertent administration of excessive doses of paracetamol by using multiple paracetamol-containing products at once, such as cough and cold remedies, analgesics or arthritic formulations, antipyretics or products for relief of menstrual symptoms or muscle spasm. Administration of paracetamol to children may be especially prone to error due to the many concentrations and strengths of products available. To avoid dosing errors, all product labels should be checked carefully to ensure calculation of the amount of paracetamol to be given.

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.

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.
- Anticoagulant dosage may require reduction if paracetamol medication is prolonged.
- Paracetamol absorption is increased by medicines that increase gastric emptying, e.g. metoclopramide or by domperidone, and decreased by medicines that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties and narcotic analgesics or by cholestyramine. Oral doses of cholestyramine and paracetamol should be given at least 1 hour apart.
- Paracetamol may increase chloramphenicol concentrations.

- The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant medicines, hepatic enzyme-inducing Agents (e.g., barbiturates, carbamazepine, phenytoin) and hepatotoxic medications. Concurrent administration of enzyme inducers and paracetamol may decrease the therapeutic effect of paracetamol, probably because of increased metabolism resulting from induction of hepatic microsomal enzyme activity.
- Chronic high-dose administration of paracetamol with salicylates and/or other non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of analgesic nephropathy.
- Paracetamol/Zidovudine: Paracetamol may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine. Zidovudine may also inhibit the hepatic glucuronidation of paracetamol. Concurrent use should be avoided, because the toxicity of either or both medications may be potentiated.

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.

- 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").

- Hepatotoxicity (see Section 4.4 – "Special warnings and precautions for use")
- nephropathy, including papillary renal failure has been reported following consumption of large amounts of paracetamol. Renal tubular necrosis has been associated occasionally with hepatic injury produced by paracetamol overdose.

Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed nor refuted:

- dyspepsia
- nausea
- hypersensitivity reactions including skin eruptions, laryngeal edema, bronchospasm, and/or anaphylaxis have occurred rarely. Dose-dependent cross-sensitivity to paracetamol may occur in aspirin-sensitive asthmatics. Low initial doses of paracetamol (less than 1000 mg) are recommended in these patients, with monitoring for about 3 hours following initial doses.
- haematological reactions (neutropenia and thrombocytopenia purpura have been reported and rarely agranulocytosis).

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.

Overdose of paracetamol can result in severe liver damage and sometimes 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: Toxic symptoms following an overdose with paracetamol include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

In adults, hepatotoxicity may occur after ingestion of a single dose of paracetamol 10 to 15g; a dose of 25g 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.

Treatment
Prompt treatment is essential even when there are no obvious symptoms.
In cases of overdosage, methods of reducing absorption of ingested medicine are important.
Prompt administration of activated charcoal 50 g in 150 mL of water and 150 mL sorbitol 50% solution by mouth may reduce absorption. It is recommended that intravenous fluids such as normal saline be given concurrently. Gastric lavage is indicated if the patient is unwilling or unable to drink an activated charcoal/sorbitol mixture.

If the history suggests that paracetamol 150 mg/kg body weight or 15 g total or more has been ingested, administer the following antidote:

Intravenous acetylcysteine 20%: Administer acetylcysteine immediately without waiting for positive urine test or plasma level results if 8 hours or less since overdose ingestion. Initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in glucose 5% 500 mL over four hours and

100 mg/kg in glucose 5% 1 L over 16 hours. If more than eight hours have elapsed since the overdose was taken, the antidote may be less effective.

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

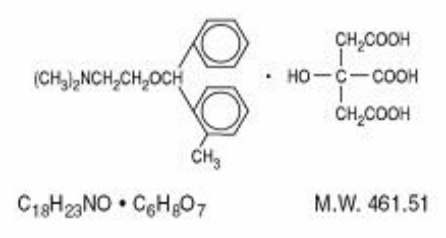
Orphenadrine citrate is white or almost white, crystalline powder. It is sparingly soluble in water, and slightly soluble in alcohol. Paracetamol is a white or almost white, crystalline powder that is sparingly soluble in water and freely soluble in alcohol.

Chemical structure

Orphenadrine citrate

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

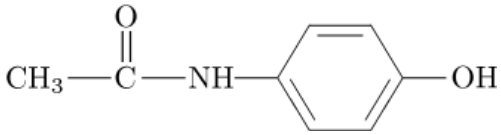
Chemical structure:



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 Pharmaceutical Industries Ltd.
P.O.Box 3190, Petach-Tikva

8. REGISTRATION NUMBER

018.08.20537

The leaflet was revised in May 2021 accroding to MOHs guidelines