PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

LENASPASM 35 mg/450 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 35 mg orphenadrine citrate and 450 mg paracetamol.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LENASPASM is a white to off white, oblong shaped tablet debossed with "E 47" on one side and a break line on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LENASPASM is indicated in adults for:

- The treatment of generalised mild to moderate pain and/or fever.
- The relief of muscle spasm associated with acute painful musculoskeletal conditions.

4.2. Posology and method of administration

Posology

Adults

Take two tablets three or four times a day.

DO NOT EXCEED THE RECOMMENDED DOSE.

Paediatric population

Not recommended for children under 18 years of age.

Do not use continuously for more than 10 days without consulting your doctor.

Method of administration

For oral administration.

4.3. Contraindications

LENASPASM is contraindicated in:

- Patients with hypersensitivity to paracetamol, orphenadrine citrate or to any excipients in LENASPASM (see section 6.1).
- Patients with severe liver function impairment.
- Patients with prostatic enlargement or obstruction of the bladder neck.
- Patients with cardio-spasm.
- Patients suffering from paralytic ileus, pyloric or duodenal obstruction, stenosing peptic ulcers or pyloric stenosis where the use of LENASPASM may lead to an obstruction.
- Patients with glaucoma.
- Patients with porphyria.

- Patients with myasthenia gravis.
- Patients when the ambient temperature is high, due to the risk of provoking hyperpyrexia.

4.4. Special warnings and precautions for use

LENASPASM contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Do not take with any other paracetamol-containing products.

Hepatic conditions

Dosage in excess of the recommended dose may cause severe liver damage. LENASPASM is contraindicated in patients with liver failure (see section 4.3). The hazard of overdose of paracetamol, as in LENASPASM, is greater in those with non-cirrhotic alcoholic liver disease.

Patients suffering from liver disease should take paracetamol under medical supervision.

Elderly population

LENASPASM should be used with caution in elderly men due to the possibility of prostatic enlargement (see section 4.3).

Cardiovascular conditions

LENASPASM should be used with caution in conditions characterised by tachycardia such as hyperthyroidism, cardiac decompensation, cardiac dysrhythmias, cardiac insufficiency or failure, and in cardiac surgery.

Renal conditions

Caution should be used when initiating treatment with LENASPASM in patients with urinary retention. Patients suffering from kidney disease should take paracetamol under medical supervision.

Euphoriant effect

Orphenadrine, as in LENASPASM has been abused for supposed euphoriant effect. The mood elevating effects may occur at therapeutic doses of orphenadrine as in LENASPASM.

4.5. Interaction with other medicines and other forms of interaction

Orphenadrine, as contained in LENASPASM, may increase central nervous system depression if taken concurrently with alcohol or central nervous system depressants. Caution is recommended in patients on other central nervous depression-producing medication**.**
The likelihood of paracetamol, as contained in LENASPASM, toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant medicines.

Cholestyramine

The concomitant administration of LENASPASM and cholestyramine may reduce the absorption of paracetamol, as contained in LENASPASM.

Anticholinergic medicines

The effect of LENASPASM may be enhanced by the concomitant administration of other medicines with anticholinergic properties such as amantadine, some antihistamines, butyrophenones and phenothiazine antipsychotics and tricyclic antidepressants

Monoamine oxidase inhibitors

Inhibition of medicine metabolising enzymes by monoamine oxidase inhibitors (MAOIs) may possibly enhance the effects of orphenadrine, as contained in LENASPASM.

Cisapride, domperidone, metoclopramide

Antimuscarinics, such as orphenadrine, as contained in LENASPASM, may antagonise the gastrointestinal effects of cisapride, domperidone, and metoclopramide. The rate of absorption of paracetamol, as contained in LENASPASM, may be increased by metoclopramide or domperidone.

Paracetamol as contained in LENASPASM, absorption is decreased by medicines that decrease gastric emptying. The rate of absorption of paracetamol, as contained in LENASPASM, may be decreased by propantheline, antidepressants with anticholinergic properties and narcotic analgesics.

Paracetamol as contained in LENASPSM may increase chloramphenicol concentrations.

Bupropion

Orphenadrine, as contained in LENASPASM, is an inhibitor of the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of bupropion to its major metabolite. LENASPASM should be used with caution in patients also receiving bupropion.

Anticoagulants

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol, as contained in LENASPASM, with increased risk of bleeding, however occasional doses have no significant effect.

Chlorpromazine

Orphenadrine, as contained in LENASPASM, may decrease the plasma concentration of chlorpromazine, possibly by interfering with absorption from the gastrointestinal tract.

Parasympathomimetics

Antimuscarinics medicines, such as orphenadrine, and parasympathomimetics may counteract each other's effects.

Effects of LENASPASM on absorption

The reduction in gastric motility caused by antimuscarinics such as orphenadrine, as contained in LENASPASM, may affect the absorption of other medicines.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safe use in pregnancy has not been established, therefore LENASPASM should not be used in pregnant women.

Animal reproduction studies have not been conducted with orphenadrine, as contained in LENASPASM. It is also not known whether orphenadrine, as contained in LENASPASM, can

cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Lactation

Safety in lactation has not been established. LENASPASM should not be taken during lactation as orphenadrine and paracetamol are excreted into breast milk.

Fertility

No data available

4.7. Effects on ability to drive and use machines

Since adverse reactions such as dizziness, syncope, light-headedness and blurred vision have been reported in patients receiving LENASPASM, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LENASPASM does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

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

Paracetamol

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Blood dyscrasias including thrombocytopenia, agranulocytosis, neutropenia, pancytopenia, leukopenia
Immune system disorders			Hypersensitivity (including skin rash that is usually erythematous or urticarial, sometimes accompanied by fever and mucosal lesions), anaphylactic shock, angioedema
Gastrointestinal disorders		Pancreatitis	
Skin and subcutaneous tissue disorders		Toxic Epidermal Necrolysis (TEN), *Stevens*-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption	

Orphenadrine citrate

System organ class	Frequency unknown (cannot be estimated from the available data)
Blood and the lymphatic system disorders	Aplastic anaemia
Immune system disorders	Hypersensitivity reactions
Metabolism and nutrition disorders	Thirst
Psychiatric disorders	Insomnia, mental confusion (especially in the elderly), drowsiness, hallucinations, agitation
Nervous system disorders	Staggering, light-headedness, giddiness

	Tremor,
	Dizziness, headache
Eye disorders **Ear and labyrinth disorders**	Dilation of the pupils, loss of accommodation, photophobia, increased intraocular pressure,
	Blurred vision, increased ocular tension
Cardiac disorders	Transient bradycardia, followed by tachycardia, with palpitations and dysrhythmias
Vascular disorders	Flushing,
	Syncope
Respiratory, thoracic and mediastinal disorders	Reduced bronchial secretion may be associated with the formation of mucus plugs
Gastrointestinal disorders	Dry mouth with difficulty swallowing, reduction in the tone and motility of the gastrointestinal tract leading to constipation, vomiting, retrosternal pain due to increased gastric reflux,
	Nausea, gastric irritation
Skin and subcutaneous tissue disorders	Dryness of the skin, pruritus, urticaria and other dermatoses
Renal and urinary disorders	Desire to urinate with the inability to do so, urinary hesitancy, urinary retention
General disorders and administrative site conditions	Weakness

c) Other special populations

Persons with Down's syndrome appear to have an increased susceptibility to the anticholinergic type action with orphenadrine as contained in LENASPASM, whereas those with albinism may be resistant.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:
E-mail: Drugsafety@aspenpharma.com
Tel: 0800 118 088

4.9. Overdose

Symptoms

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed. Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, eating disorders, starvation, cachexia, cystic fibrosis and with the use of medicines that induce liver microsomal oxidation such as barbiturates (e.g. phenobarbitone), isoniazid, rifampicin, phenytoin, carbamazepine, primidone and St. John's Wort. Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic

dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage.

Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Orphenadrine

Orphenadrine, as contained in LENESPASM is toxic when overdosed and typically induces anticholinergic effects. The minimum lethal dose is 2 to 3 grams for adults, however the range of toxicity is variable and unpredictable. Tachycardia, rapid or stertorous respiration, hyperpyrexia, restlessness, confusion, excitement and hallucinations passing into delirium. A rash on the face and upper trunk may appear. In severe intoxication, depression of the central nervous system may occur with hypertension or circulatory failure and respiratory depression.

Treatment

Paracetamol

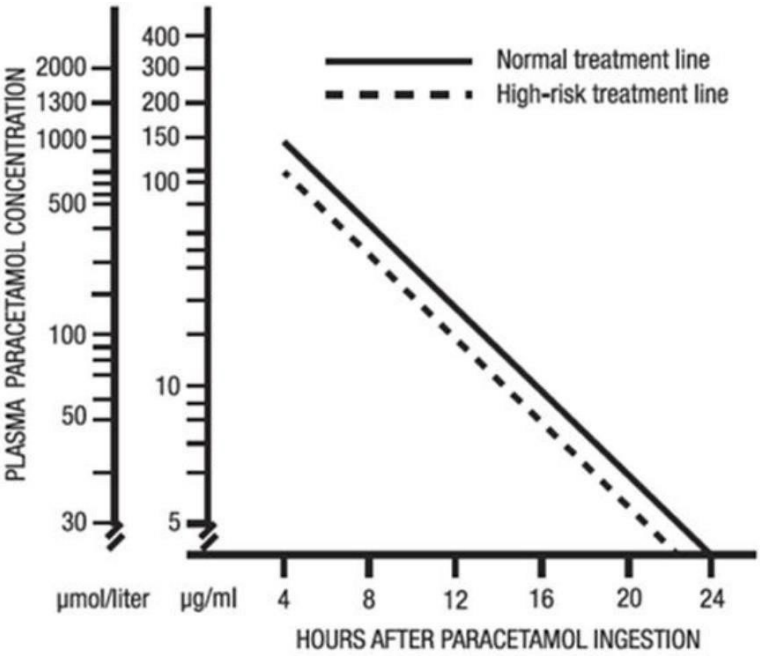
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours**. The volume of intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.
A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.
Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.
Monitor all patients with significant ingestions for at least ninety six hours.

Paracetamol nomogram

Notes for the use of the nomogram:

- Patients with plasma paracetamol concentrations on or above the normal treatment line should be given acetylcysteine.
- For high-risk patients (e.g. those taking enzyme inducing medicines, alcohol abusers or glutathione-depleted patients) use the high-risk treatment line.
- The nomogram should be used in relation to a single acute ingestion only.



Orphenadrine

Treatment is symptomatic and intensive monitoring and appropriate treatment of any emergent anticholinergic effects. Institution of haemodialysis or peritoneal dialysis may be of some benefit if the serum concentration exceeds 4 mcg per 4ml.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: e.g. Muscle relaxants, centrally acting agents, orphenadrine, combinations.

ATC code: M03BC51

Mechanism of action

Paracetamol

Paracetamol, as contained in LENASPASM, has analgesic and antipyretic properties. Its mechanism of action is not fully understood. It has been suggested that it may act predominantly by inhibiting prostaglandin synthesis in the CNS and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation. Paracetamol probably produces an antipyretic action by a central effect on the hypothalmic heat-regulating centre to produce peripheral vasodilatation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. Paracetamol has only weak anti-inflammatory effects, and it has been thought to have a generally poor ability to inhibit COX in the presence of high concentrations of peroxides, as are found at sites of inflammation. This aspect of its action has not been addressed rigorously. A dose of 1000 mg results in ~50 % inhibition of both COX-1 and COX-2 in whole blood assays.

Orphenadrine

Orphenadrine, as contained in LENASPASM, is an anticholinergic medicine. It also has weak antihistaminic, local anaesthetic and skeletal relaxant properties.

Orphenadrine, as contained in LENASPASM, which is a congener of diphenhydramine without sharing its soporific effect, is a tertiary amine antimuscarinic with actions similar to those of trihexyphenidyl. Orphenadrine is used as a citrate to relieve pain due to skeletal muscle spasm.

5.2. Pharmacokinetic properties

Paracetamol

Absorption

Oral paracetamol has excellent bioavailability. Peak plasma concentrations occur within 30 to 60 minutes and the t ½ in plasma is ~2 hours after therapeutic doses.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the medicine to plasma proteins is variable but less than with other NSAIDs. Only 20 % to 50 % is bound at the concentrations encountered during acute intoxication.

Biotransformation

Elimination occurs primarily after hepatic conjugation with glucuronic acid (~ 60 %), sulfuric acid (~ 35 %), or cysteine (~ 3 %); small amounts of hydroxylated and deacetylated metabolites also have been detected. Children have less capacity for glucuronidation of the medicine than do adults. A small proportion of paracetamol undergoes CYP-mediated N-hydroxylation to form NAPQI, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione (GSH) and thereby is rendered harmless.
However, after ingestion of large doses of paracetamol, the metabolite is formed in amounts sufficient to deplete hepatic GSH and contributes significantly to the toxic effects of overdose.

Elimination

Some 90 % to 100 % of the medicine may be recovered in the urine within the first day at therapeutic dosing.

Orphenadrine

Absorption

Orphenadrine is readily absorbed from the gastrointestinal tract.

Biotransformation

Orphenadrine is almost completely metabolised to at least eight metabolites.

Elimination

Orphenadrine is mainly excreted in the urine as metabolites and small amounts of unchanged medicine. The half-life of orphenadrine has been reported to be 14 hours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

PVC/PE/PVDC/Al blisters with 12 tablets per blister strip. Two or four blister strips are packed into a carton in pack sizes of 24 or 48.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

49/2.9/0441

9. DATE OF FIRST AUTHORISATION

15 March 2022

10. DATE OF REVISION OF TEXT

15 March 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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