PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S2**

1. NAME OF THE MEDICINE

UNIFLEX 450 mg / 35 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains:

Paracetamol	450 mg
Orphenadrine citrate	35 mg

Sugar free.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White, circular, biconvex tablets with a breaker on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

UNIFLEX tablets are indicated for generalised pain and the relief of muscle spasm associated with acute painful musculo-skeletal conditions.

4.2 Posology and method of administration

Posology

Adults: 2 tablets 3 times a day.

DO NOT EXCEED THE RECOMMENDED DOSAGE

Method of administration

Oral.

4.3. Contraindications

- Hypersensitivity to any of the ingredients.
- Severe liver function impairment.
- Prostatic enlargement, achalasia, bladder neck obstruction, glaucoma, myasthenia gravis, peptic ulcer or stenosing and pyloric or duodenal obstruction.
- Patients with porphyria.

4.4 Special warnings and precautions for use

This product 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.

- Dosages in excess of those recommended may cause severe liver damage.
- Patients suffering from liver or kidney disease should take **UNIFLEX** under medical supervision.
- Caution is recommended in patients on other central nervous system depression-producing medication as well as patients on anticholinergics or medication with anticholinergic properties.
- Use with caution in patients with cardiac disease or arrhythmias, especially tachycardia.
- Do not use continuously for more than 10 days without consulting your doctor.
- Severe cutaneous adverse reactions (SCARs):

  Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with UNIFLEX must immediately be discontinued and appropriate treatment instituted (see Section 4.8).

4.5 Interaction with other medicines and other forms of interactions

Orphenadrine

Orphenadrine may increase central nervous system depression if taken concurrently with alcohol or central nervous system depressants. Anticholinergic effects may be intensified if orphenadrine is taken concurrently with anticholinergics or medication with anticholinergic effects.

Paracetamol

Alcohol or Hepatic enzyme inducers or Hepatotoxic medications:

Risk of hepatotoxicity with single toxic doses or prolonged use of high doses of paracetamol may be increased in alcoholics or in patients taking other hepatotoxic medications or hepatic enzyme inducers.

Chronic use of barbiturates (except butalbital) or primidone has been reported to decrease the therapeutic effects of paracetamol.

Anticoagulants, coumarin or indandione derivative:

Concurrent chronic, high-dose administration of acetaminophen may increase the anticoagulant effect, possibly by decreasing hepatic synthesis of procoagulant factors.

Anti-inflammatory medicines, nonsteroidal (NSAIDs) or Aspirin or other salicylates.

Prolonged concurrent use of paracetamol and a salicylate significantly increases the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal disease, and cancer of the kidney or urinary bladder.

Prolonged concurrent use of acetaminophen and NSAIDs other than aspirin may also increase the risk of adverse renal effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in breastfeeding has not been established.

Fertility

Safety in fertility has not been established.

4.7 Effects on ability to drive and use machines

This medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Frequency	**System organ class**	**Undesirable effects**
Frequency not known (cannot be estimated from the available data)	Blood and lymphatic system disorders	Thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis and anemia.
	Cardiac disorders	Transient bradycardia followed by tachycardia, with palpitations and arrhythmias
	Eye disorders	Dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia
	Gastrointestinal disorders	Pancreatitis. Dryness of the mouth with difficulty in swallowing and talking, thirst. Reduction in the tone of motility of the gastro-intestinal tract leading to constipation and occasionally vomiting.
	Hepato-biliary disorders:	Hepatitis
	Nervous system disorders:	Confusion, giddiness and staggering
	Psychiatric disorders	Insomnia
	Renal and urinary disorders:	Difficulty in micturition Renal colic, renal failure, sterile pyuria
	Respiratory, thoracic and mediastinal disorders	Reduced bronchial secretions
	Skin and subcutaneous tissue disorders:	Skin rashes and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial but sometimes

		more serious and may be accompanied by fever and mucosal lesions. Dryness of the skin. Fixed drug eruptions (FDE) (see Section 4.4).
	Vascular disorders:	Flushing of the skin
	Immune system disorders:	Drug-induced hypersensitivity syndrome (DIHS), hypersensitivity reactions characterised by urticaria, dyspnoea, and hypotension (see Section 4.4).

Post-marketing experience:

The following side effects have been reported and frequencies are unknown:

Fixed drug eruptions (FDE) and drug-induced hypersensitivity syndrome (DIHS) (see Section 4.4).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

One may also report to Adcock Ingram Limited using the following email: Adcock.AEReports@adcock.com

4.9 Overdose

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 -10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

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 arrhythmias have been reported.

Treatment for paracetamol overdosage:
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. For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity. Monitor all patients with significant ingestions for at least ninety-six hours.

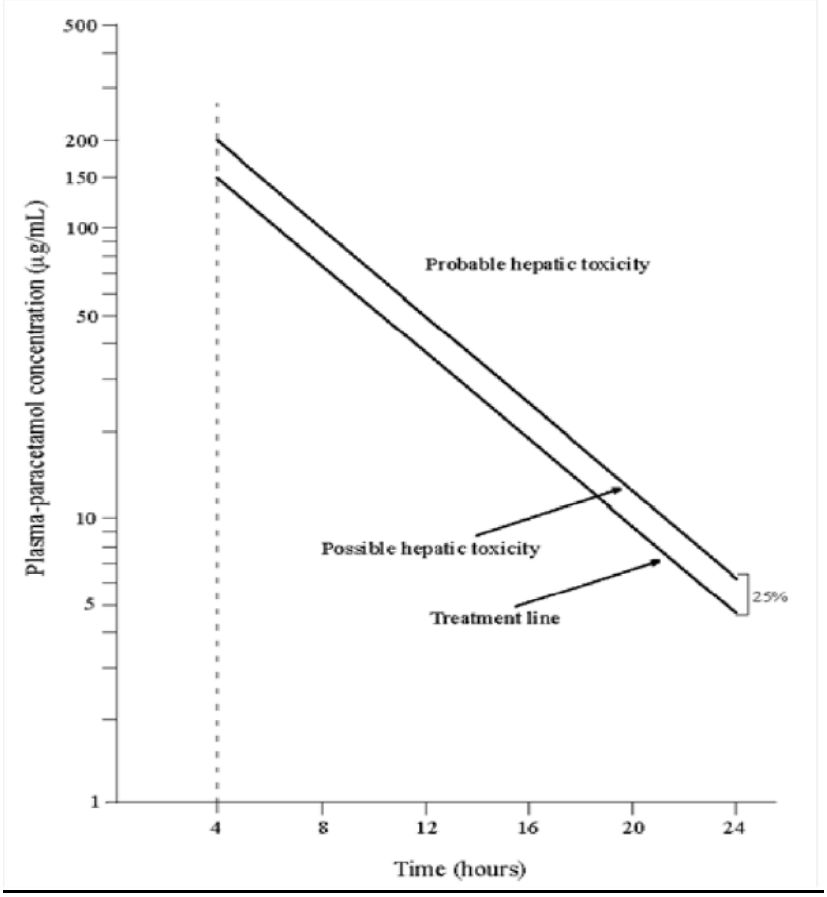

Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.

Orphenadrine citrate:

Toxic doses cause tachycardia, rapid respiration, hyperpyrexia and central nervous system stimulation marked by restlessness, confusion, excitement, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures or convulsions. A rash may appear on the face or upper trunk. In severe intoxication, central stimulation may give way to central nervous system depression, coma, circulatory and respiratory failure, and death. Treatment is symptomatic and supportive. Institution of hemodialysis or peritoneal dialysis may be of some benefit if the serum concentration exceeds 4 mcg per 4 ml.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.8 Analgesic combinations

Mechanism of action

UNIFLEX tablets have analgesic, antipyretic and skeletal muscle relaxant properties.

Paracetamol:

Paracetamol has analgesic and antipyretic effects. It 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. It has been suggested that COX inhibition might be disproportionately pronounced in the brain, explaining its antipyretic efficacy.

Orphenadrine citrate:

Orphenadrine citrate is a muscle relaxant acting in the CNS, having, in general, a depressant effect. Orphenadrine also has anticholinergic properties.

5.2 Pharmacokinetic properties

Paracetamol

Oral paracetamol has excellent bioavailability. Peak plasma concentrations occur within 30 – 60 minutes, and the t1/2 in plasma is about 2 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable but less than with other NSAIDs; only 20 – 50 % is bound at the concentrations encountered during acute intoxication. Some 90 – 100 % of the drug may be recovered in the urine within the first day at therapeutic dosing, primarily after hepatic conjugation with glucuronic acid (about 60 %), sulfuric acid (about 35 %), or cysteine (about 3 %); small amounts of hydroxylated and deacetylated metabolites have also been detected.

Orphenadrine citrate

Orphenadrine is readily absorbed from the gastrointestinal tract and after intramuscular injection. It is almost completely metabolised to at least 8 metabolites. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. The half-life of orphenadrine has been reported to be 14 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulphate, sodium starch glycolate and stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

6.5 Nature and contents of container

Cartons containing polyvinyl chloride (PVC) / aluminium blister packs of 20's, 50's, 100's and 120 tablets. Polypropylene securitainers with low-density polyethylene (LDPE) closures containing 50 and 100 tablets. White screw type HDPE container with white high-density polyethylene (HDPE) screw cap containing 120 tablets.

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Marketed by:
Unicorn Pharmaceuticals (Pty) Ltd
Corner of Searle and Pontac Streets,
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8. REGISTRATION NUMBER

32/2.8/0605

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 August 2000

10. DATE OF REVISION OF THE TEXT

16 February 2024