SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Unigesic (35 + 450) mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White, standard convex bisect two-layer tablets with a diameter of 12.0 mm ± 0.6%.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Unigesic is indicated for:
- Painful post-traumatic muscle syndromes.
- Muscle contractions caused by sudden body movements.
- Sprains.
- Extra-articular rheumatism accompanied by muscle spasm (fibrositis, myositis, myalgia).
- Acute or chronic low back pain (lumbago).

4.2. Posology and method of administration

Posology

Adults
1-2 tablets 3 times daily or as determined depending on the patient's condition.

Elderly
The dose in patients over 65 years of age should not exceed 3 tablets daily (105 mg orphenadrine citrate daily). The usual dose is ½-1 tablet 3 times daily (see section 4.4).

Paediatric population
No data available. The safety and efficacy of Unigesic in children 0 to 12 years of age have not yet been established.

Treatment duration
The duration of treatment will generally vary to a maximum of 10 days, depending on the patient's condition.

Method of administration
The tablets can be divided into two equal doses. The tablets should be swallowed with a glass of water. The tablets can be taken with or without food.

4.3. Contraindications

Unigesic is contraindicated in:
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Glaucoma, urinary retention (e.g. prostatic hyperplasia or bladder neck obstruction), severe myasthenia (myasthenia Gravis) or gastrointestinal obstruction, e.g. pyloric and duodenal stenosis, stenosing peptic ulcer, megaesophagus, due to the parasympatholytic action of orphenadrine.
- Severe hepatic and severe renal impairment due to paracetamol.
- Breast-feeding (see section 4.6).
- Children under 12 years of age.

4.4. Special warnings and precautions for use

Orphenadrine
Unigesic should be used with caution in patients with tachycardia, coronary heart disease, palpitations, dry mouth, high intraocular pressure, constipation and urticaria.

Euphoria has been reported in patients amenable to treatment.
In long-term use of orphenadrine or in high doses, periodic hematological, renal and hepatic monitoring is considered necessary.

Paracetamol
Unigesic should not be combined with other medicinal products containing paracetamol to prevent overdose. The recommended doses should not be exceeded. Higher doses than those recommended carry a risk of very serious liver damage. Clinical signs of the liver damage usually does not appear until a couple of days and usually after 4-6 days. The antidote should be given as early as possible (see section 4.9). Caution is advised when administering paracetamol to patients with renal impairment, hepatic impairment or patients with chronic alcohol abuse. In chronic malnutrition, the glutathione supply decreases and the dose of Unigesic should be reduced.

Unigesic should be used with caution in elderly patients. Precautions and contraindications have a special effect in elderly patients. Orphenadrine, like other anticholinergic drugs, can cause confusion and delirium in the elderly (see section 4.2).

Due to the interaction of anesthetics with orphenadrine, caution should be taken in surgeries or dental procedures in patients receiving this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Orphenadrine
The concomitant use of orphenadrine with other Central Nervous System depressants such as alcohol, barbiturates, opioids and anesthetics may increase the suppression of the Central Nervous System resulting in e.g. respiratory depression and sedation. Possible cumulative effect may occur when orphenadrine is co-administered with other medicinal products who have anticholinergic properties i.e. atropine, phenothiazines. Co-administration of orphenadrine and phenothiazines may lead to a decrease in plasma concentration of phenothiazines.

Antihistamines, antispasmodics, tricyclic antidepressants, phenothiazines, dopaminergic antiparkinson drugs including amantadine, quinidine and antiarrhythmic agents such as disopyramide may increase the anticholinergic effect of orphenadrine. The anticholinergic effect of orphenadrine on the gastrointestinal tract may lead to decreased gastrointestinal motility, which may affect the absorption of other orally administered drugs.

The antiparkinsonian activity of L-DOPA can be increased by orphenadrine.

Concomitant use of orphenadrine and chlorpromazine is associated with an increased risk of hypothermia.

Paracetamol
Cholestyramine decreases the absorption of paracetamol while metoclopramide and domperidone increases the absorption.

Concomitant use of drugs that induce liver enzymes (such as phenobarbital) or may be hepatotoxic (e.g. NSAIDs, interferons) increases the risk of liver damage.

Patients taking barbiturates, tricyclic antidepressants, and alcohol may experience metabolism disorders of high doses of paracetamol and increase plasma half-life of paracetamol.

Probenecid may decrease renal excretion and increase plasma paracetamol levels.

Concomitant administration of oral anticoagulants (e.g. warfarin) appears to increase the risk of bleeding. The combination justifies a more intensive monitoring of INR at the beginning and at the finish of such maintenance treatment.

Long-term oral use of antiepileptics (phenytoin, phenobarbital, carbamazepine) or steroid contraceptives affect liver enzymes and prevent therapeutic plasma levels from being achieved by increasing first-pass metabolism or elimination.

Concomitant use of paracetamol and zidovudine increases the appearance of neutropenia. This medicine should be used concomitantly with zidovudine only after medical advice.

Salicylamide causes a prolongation of the elimination half-life of paracetamol, accumulation and formation of hepatotoxic metabolites.

Co-administration of chloramphenicol leads to a 5-fold increase in the elimination half-life of chloramphenicol.

Laboratory tests: Paracetamol may give false blood uric acid results by phospho-wolframic acid method and glucose results by oxidase-peroxidase method.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Unigesic should not be used during pregnancy unless the clinical condition of the woman requires treatment with the medicinal product.

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, however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding
Orphenadrine and paracetamol are excreted in human milk. Unigesicis contraindicated during breast-feeding (see section 4.3).

Fertility
There are no available data.

4.7. Effects on ability to drive and use machines

Orphenadrine may cause dizziness and blurred vision and therefore may affect the ability to drive and use machines. Patients should be advised to avoid driving and operating machinery if such effects occur.

4.8. Undesirable effects

It is estimated that approximately 15% of treated patients have reported adverse reactions. Adverse reactions are mainly associated with the parasympatholytic effect of orphenadrine.

Adverse reactions are listed below, sorted by MedDRA system organ class and frequency.
Frequencies are defined as follows:

Very common (≥ 1/10);
Common (≥ 1 /100 to < 1/10);
Uncommon (≥ 1/1,000 to <1/ 100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000);
Not known (Cannot be estimated from the available data).

System organ class	**Common**	**Rare**	**Very rare**	**Not known**
Psychiatric disorders			Hallucinations, confusion	Anxiety
Nervous system disorders			Tremor	Headache
Eye disorders	Blurred vision		Accommodation disorder	Increase of the intraocular pressure, mydriasis
Cardiac disorders			Palpitations	Tachycardia, fainting
Gastrointestinal disorders	Nausea, dry mouth		Constipation	Vomiting
Hepatobiliary disorders		Hepatic failure		
Renal and		Increased creatinine	Urinary retention	

urinary disorders				
Skin and subcutaneous tissue disorders		Rash, urticaria, angioedema	Severe skin reactions (e.g. Steven-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis)	
Blood and lymphatic system disorders				Aplastic anaemia
General disorders and administration site conditions	Fatigue, dizziness	Allergic reaction		Weakness, heaviness of head

Hepatic failure from paracetamol use has been reported in association with alcohol abuse. In long-term use, the risk of renal failure cannot be excluded.

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal .

4.9. Overdose

Orphenadrine

Toxicity

In adults and children from 2 years of age, a dose of orphenadrine 1.0 to 4.5 g and 0.7 to 1.0 g, respectively, has been reported to be fatal. A 3.5-year-old child received 25-50 mg, a dose that caused moderate to severe symptoms of poisoning.

Symptoms

Cardiac and CNS toxicity are major risks. Central and peripheral anticholinergic symptoms may persist for several days. Symptoms of overdose of orphenadrine citrate include agitation, confusion, hyperreflexia, hallucinations and delirium leading to rapid onset of coma. Dry mucous membranes, dilated pupils, convulsions, cerebral edema, respiratory depression, apnoea may occur. Also, tachycardia, bradycardia and atrioventricular block, abdominal arrhythmias, drop in blood pressure, cardiogenic shock or pulmonary edema. Hypoglycaemia, hypokalaemia, anuria, oliguria, hepatic impairment and urinary retention may occur.

Treatment
Apply immediately gastric lavage, independently from the dose that is estimated to have been administered. Apply activated charcoal, laxatives while intensive monitoring should be performed. Provide ventilator therapy if necessary. Correct hypoglycaemia, hypokalaemia and acidosis. Spasms and delirium are treated with relatively high doses of diazepam, preferably orally. Avoid barbiturates. In case of heart failure and drop in blood pressure, an injection of dobutamine, dopamine or prenalterol (avoid the administration of adequate amounts of fluid due to the risk of cerebral edema) should be administered. Lidocaine (50-100 mg) as bolus injection, followed by an infusion of 1-3 mg per minute can be used in ventricular arrhythmias and isoprenaline injection or a pacemaker in torsade de pointes ventricular tachycardia. Physostigmine (dose 1-2 mg slowly intravenously; children 0.02-0.04 mg / kg) can be given for central anticholinergic symptoms, but treatment should be given only after 16 hours and only if tachycardia occurs at the same time.

Paracetamol

Toxicity
Paracetamol overdose can cause acute hepatic failure, the symptoms of which may not appear for several days after ingestion. Ingestion of a single dose of 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis.

Symptoms
Symptoms of paracetamol overdose appear within 24 hours and become severe. These include nausea, vomiting, hyperhidrosis, lethargy and abdominal pain. After 2-3 days there are signs of liver failure: increased levels of transaminases, decreased prothrombin levels, collagen disease, jaundice, general malaise, hypoglycaemia, hypocalcaemia, hypophosphatemia, metabolic acidosis, generalized cerebral palsy, encephalopathy, hepatic coma and fatal outcome. Liver failure usually peaks in 4-6 days.

Acute renal failure can occur from acute tubular necrosis even without severe hepatic impairment. Myocardial damage and pancreatitis may also occur.

Treatment
It is recommended that the patient should be transported to a hospital, in order to check in time the levels of paracetamol in plasma. If treatment starts immediately within 8-10 hours with N-acetylcysteine, L-methionine or L-cystamine, the liver injury is minimized. In severe cases, a liver transplant may be necessary.

Hemodialysis and hemofiltration may reduce the plasma concentration of paracetamol. Forcing urination is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Orphenadrine, Combinations, ATC code: M03BC51

Orphenadrine acts centrally, by inhibiting the facilitatory mechanisms of the reticular formation i.e. selectively inhibits those pathways whose overstimulation leads to an increase of the kinetic functions, such as spasticity, stiffness or muscle spasm. Orphenadrine relaxes only the muscle spasm without negatively affecting the normal muscle tone or the normal voluntary movements. The action of orphenadrine to skeletal muscle spasms have been proved with electromyography.

Paracetamol is a well-tolerated analgesic and antipyretic. It is proved that is particularly efficient in pain relief of muscles and joints. In paracetamol, the mechanism of analgesic action has not been fully determined. Paracetamol can act mainly by inhibiting the synthesis of prostaglandins in the central nervous system and to a lesser extent through a peripheral action, inhibiting the production of pain pulse. Paracetamol does not cause gastric irritation or hemorrhage. Liver and renal necrosis have been associated with orally administrated paracetamol in higher doses than the usual therapeutic dosage.

5.2. Pharmacokinetic properties

Absorption

Orphenadrine
Orally administered orphenadrine is rapidly and almost completely absorbed (> 70%). Peak plasma concentrations are reached after 2-4 hours. There is some evidence that concentrations after multiple doses are higher than those predicted by a single dose. There are no signs of accumulation or saturation.

Paracetamol
Oral paracetamol has a high bioavailability of about 90%. Peak plasma concentrations are reached within 30-60 minutes.

Distribution

Orphenadrine
Low plasma concentration due to rapid distribution in tissue compartments.

Paracetamol
Paracetamol is relatively evenly distributed in most body fluids. The binding of drug with plasma proteins is variable but less than with other NSAIDs (10% -25%) at normal therapeutic concentration, but increases with higher concentrations.

Biotransformation

Orphenadrine
Orphenadrine is almost completely metabolized, as indicated by the recovery of only 8% of the administered dose as unchanged drug in the urine. The liver appears to be the major site of the metabolism of orphenadrine.

Paracetamol
Paracetamol is metabolized in the liver primarily by conjugation to glucuronic acid (approximately 60%), sulfuric acid (approximately 35%) or cysteine (approximately 3%). Small quantities of hydroxylated and deacetylated metabolites have also been detected. The hydroxylated metabolite, which is usually produced in very small quantities by mixed function oxidases of the liver and which is usually detoxified by conjugation to liver glutathione, may accumulate after paracetamol overdose and cause liver damage.

Elimination

Orphenadrine
The elimination half-life of orphenadrine ranged from 13-20 hours (mean 15.5 hours) after single dose administration to healthy volunteers. After long-term treatment in patients, the half-life was

increased to 30-40 hours. The small quantity of unchanged orphenadrine as well as of its metabolites are mainly excreted (> 60%) in the urine.

Paracetamol
Approximately 90-100% of the drug can be recovered in the urine within the first day following a therapeutic dose. The elimination half-life ranges from 1-4 hours. In patients with severe renal impairment (creatinine clearance <10 ml/minute) the elimination of paracetamol is slightly delayed and metabolites may accumulate.

5.3. Preclinical safety data

Orphenadrine
In vitro studies have shown no evidence of clinically significant mutagenic potential of orphenadrine. Not enough information is available on the potential of tumour production. The effects on the reproductive toxicological effects of orphenadrine are unstable and the embryotoxic effect of orphenadrine cannot be excluded.

Paracetamol
Extensive studies have shown no evidence of genotoxic risk in therapeutic doses of paracetamol. Long-term studies in rats and mice have not shown signs of relative oncogenic effect of non-hepatotoxic doses of paracetamol. Paracetamol crosses the placenta.

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

Maize starch
Potassium sorbate (E202)
Microcrystalline cellulose Type 101 (E460)
Starch pregelatinised (E1442)
Magnesium stearate (E572)
Silica colloidal anhydrous (E551)
Silica colloidal hydrated (E551)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5. Nature and contents of container

Each cardboard box contains 30 tablets presented in transparent PVC/Aluminum blisters, along with a Patient Information Leaflet.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.
14th km National Road 1
GR-145 64 Kifisia
Greece
Tel.: +30 210 8072512
e-mail: unipharma@uni-pharma.gr

8. MARKETING AUTHORISATION NUMBER

MA1096/00701

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2022

10. DATE OF REVISION OF THE TEXT

May 2022