NORFLEX®

(orphenadrine citrate)

Manufactured by:
Medicis Pharmaceutical Corporation
7720 N. Dobson Road
Scottsdale, AZ 85256

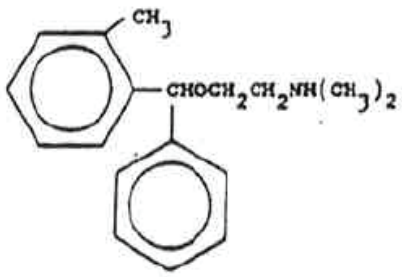
Distributed by:
Medicis Canada Ltd.,
Toronto, Ontario M5V 1Y6
Canada

Date of Preparation: January 3, 2012

Control # 152408, 152409

FACT SHEET

Norflex® Tablets and Injectable

Generic/Non-proprietary name:	Orphenadrine Citrate
Brand/Proprietary name:	Norflex®
Manufacturer:	Medicis Pharmaceutical Corporation
Chemical Name and Composition:	Tablets, 100 mg. Injectable, 60 mg/ampule. N,N-Dimethyl-2-[(O-methyl-α-phenylbenzyl) oxy] ethylamine citrate (or, the citric acid salt of orphenadrine, [2-dimethyl-aminoethyl 2-methylbenzhydryl ether]) $C_{24}H_{31}NO_8$
Structural Formula:	
Molecular Weight:	461,57
Pharmacologic Classification:	"Skeletal muscle relaxant"
Structurally Related Drugs:	Diphenhydramine analogues
What Drug is Considered Standard:	Mephenesin
Physical Properties:	The pure drug substance is a white, crystalline powder having a bitter taste and practically no odour.
Macroscopic Appearance:	Tablet – A white tablet, 11/32" diameter, standard cup
Solubility:	
Water:	Sparingly soluble
Alcohol:	Slightly soluble
Chloroform:	Insoluble
Ether:	Insoluble

Dye Content:	None
Carbohydrate Content:	Tablets – 169 mg lactose Injectable – None
Sodium Content:	Tablets – None Injectable – 2.9 mg NaCl per mL 1.0 mg Sodium Bisulfide per mL NaOH as needed to buffer to 5.5 pH
Stability:	
Recommended Storage Conditions:	Tablets: Preserve in tight, light resistant containers. Store at room temperature (below 30°C). Injectable: Preserve in original ampule. Store at room temperature (below 30 °C).
Shelf Life (Expiration Dating):	Under Above Conditions: Tablets: 5 ½ years Injectable: 5 ½ years
Site and Mechanism of Action:	Orphenadrine is a centrally acting (brain stem) compound which selectively blocks facilitatory functions of the reticular formation.
Site of Absorption:	Tablets: Primarily small bowel.
Onset of Action:	Tablets – Following a single oral dose of Norflex, onset of action has been demonstrated within one hour. Injectable – Relief is usually reported within five minutes following I.V. administration and within ten minutes following I.M. administration.
Duration of Action:	Tablets – Due to the controlled release characteristics of the tablet, Norflex usually remains active throughout a 12 hour dosing interval. Injectable – The rapid action of Norflex Injectable can be sustained by following 12 hours post-dose with Norflex tablets 1 b.i.d.
Where Metabolized:	Probably liver.
Where Excreted:	Mainly urine.
Excreted As:	Predominantly N-methyl-2-10-methy1-α-phenybenoxylethylamine and 2-(O-methyl-α-phenylbenzyloxy) ethylamine.

Toxicity:	Overdosage – Two to three grams of orphenadrine citrate orally may be lethal for adults; however, survival has followed ingestion of 8 g. The oral LD_{50} for orphenadrine citrate in mice is 150 mg/kg; by the intravenous route the LD_{50} in mice is 37 mg/kg, in rats 26 mg/kg; by intramuscular injection the LD_{50} in rats is 208 mg/kg. Symptoms – With large overdoses intoxication is very rapid, and death can occur within 2 to 12 hours preceeded by deep coma, tonic and clonic seizures, shock, and respiratory arrest. Serious cardiac rhythm disturbances are common. Treatment – Further absorption should be prevented by emesis (syrup of ipecac) and, if necessary, gastric lavage. Convulsions should be treated with diazepam or pentothal. Circulatory support should be provided as needed. Adequate renal function should be maintained. Due to rapid distribution of orphenadrine into tissues and extremely low blood levels, hemodialysis or peritoneal dialysis may not be helpful. However, when the blood level is .05 mg/dl or more hemodialysis may be worthwhile.
Does Drug Cross CNS Barrier?:	Most probably.
Indications:	Norflex is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.
Contraindications:	Because of the mild anticholinergic effect of orphenadrine, Norflex should not be used in patients with glaucoma, achalasia, prostatic hypertrophy, or obstruction of the bladder neck. Norflex is also contraindicated in patients with myasthenia gravis and in patients known to be hypersensitive to orphenadrine.
Precautions:	
General Precautions:	Orphenadrine citrate should be used with caution in patients with tachycardia, cardiac decompensation, coronary insufficiency, or cardiac arrhythmias.
Information For Patients:	Some patients may experience transient episodes of light-headedness, dizziness, or syncope, which may impair their ability to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.
Teratogenicity:	Orphenadrine has produced adverse effects at high doses in animals. In one study at five times the human daily dose, degenerative changes in

	the urinary bladder occurred in 5% of rat pups. In a subsequent study at 12 times the human daily dose, this abnormality was not observed. There are no adequate and well-controlled studies of Norflex in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Does Drug Appear in Breast Milk?:	It is not known whether orphenadrine is excreted in human milk. Caution should be exercised when Norflex is administered to a nursing woman.
Does Drug Cross Placental Barrier?:	Most probably.
Usage in Children:	Safety and effectiveness in children have not been established.
Drug/Drug Interactions:	Orphenadrine has been shown to induce enzymatic systems involving the metabolism of aminopyrine, steroidal contraceptives, griseofulvin, hexobarbital, and phenylbutazone. Orphenadrine will potentiate other anticholinergic agents. A few instance of tremors, mental confusion, and anxiety have been reported in association with concomitant propazyphene use; as these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of propoxyphene is recommended.
Drug/Lab Test Interactions:	None known.
Carcinogenesis:	No long-term studies have been performed with orphenadrine to evaluate its carcinogenic potential.
Adverse Reactions:	Adverse effects are mainly due to the mild anticholinergic action of orphenadrine, and are usually associated with higher dosage.
	Dryness of the mouth is usually the first adverse effect to appear. When the daily dose is increased, possible adverse effects include, by organ system:
	<u>Special Senses:</u> Dry mouth, blurred vision, dilation of pupils, increased intraocular tension (particularly in closed angle glaucoma).
	<u>Central Nervous System:</u> Weakness, headache, dizziness, and rarely, drowsiness, confusion (in elderly patients), hallucinations.
	<u>Cardiovascular:</u> Tachycardia, palpitation, transient syncope.
	<u>Gastrointestinal:</u> Vomiting, nausea, constipation, gastric irritation.
	<u>Urinary:</u> Hesitancy, retention.

	Hematopoietic: Rarely, aplastic anemia associated with use of orphenadrine tablets has been reported; no cause-effect relationship has been established. Immunogenic: Urticaria and other dermatoses, sometimes pruritic, have been reported in rare instances with orphenadrine administration. Rarely, anaphylactic reaction has occurred following injection of orphenadrine.
Physical Dependence:	Drug abuse and dependence have not been reported with Norflex.
Psychological Dependence:	None reported.
Tolerance:	None reported.
Potentiation of Therapeutic Effects by:	Clinical experiments have demonstrated an additive analgesic effect when APC is combined with orphenadrine citrate (Birkeland I. W. and Clawson, D. K.: Clin.Pharm. and Therap. 9:639, 1968).
Potentiation of Adverse Effects by:	Anticholinergic agents may potentiate the infrequent and usually mild anticholinergic effects of orphenadrine.
Therapeutic Advantages:	Norflex does not exert its action through a sedative mode of action as some products do. The analgesic mode of action allows Norflex to provide relief without sedation, leaving the patient alert and ambulatory. Norflex is available orally as a convenient sustained-release tablet allowing dosing 1 tablet b.i.d. for most patients. Norflex is also available in Injectable form containing a full therapeutic dose of 60 mg orphenadrine citrate in a 2 mL aqueous base allowing single site I.M. administration or I.V. administration if desired.
Therapeutic Disadvantages:	The mild anticholinergic activity of orphenadrine may cause such annoying but not serious side effects as dry mouth and blurred vision.
Dose Recommendations:	Tablets – The usual adult dose is two 100 mg. Norflex Sustained-Release Tablets per day, one in the morning and one in the evening. Injectable – The usual adult dose is 60 mg (one two mL ampule) of Norflex Injectable, administered intravenously or intramuscularly; this dose may be repeated every 12 hours. Relief may be maintained by one Norflex Tablet taken twice a day, beginning 12 hours after the last dose of Norflex Injectable.

Special Technique of Administration:	When administering Norflex Injectable intravenously, inject the drug over a period of approximately five minutes and have the patient in a supine position. Permit the patient to rest after the injection. It is advisable to assist the patient from the recumbent position after parenteral treatment. Adherence to this procedure will result in fewer adverse reactions. For intramuscular use, it is sometimes desirable to add licocaine or a similar local anesthetic to prevent pain at the site of the injection; the pH of the local anesthetic should approximate that of the drug and the resulting mixture should be used only if it remains clear.
How Supplied:	Each tablet contains orphenadrine citrate 100 mg in a sustained-release formulation. Bottles of 100. Norflex Injectable two mL glass ampules each contain orphenadrine citrate 60 mg in aqueous solution, made isotonic with sodium chloride. Boxes of six.