PRODUCT MONOGRAPH

[Pr] ARLIDIN
Nylidrin Hydrochloride tablets

Manufacturer's Standard

6 mg

Sympathomimetic agent for the relief of selected symptoms in patients with Organic Brain Syndrome / Peripheral Vasodilator

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ACTION

ARLIDIN® (nylidrin hydrochloride) acts predominantly by beta-receptor stimulation. Beta stimulation with nylidrin has been demonstrated in a variety of isolated tissues from rabbits, guinea pigs and dogs. It has been shown to dilate arterioles in skeletal muscle and to increase cardiac output in the anesthetized dog and cat and in anaesthetized man. An increase in cerebral blood flow and a decrease in vascular resistance has also been reported. The result of this combination of actions is a greater blood supply to ischemic tissues, with usually minimal change in blood pressure.

The mechanism whereby nylidrin may provide relief of selected symptoms in some elderly patients with organic brain disorders is not known.

INDICATIONS and CLINICAL USE

ARLIDIN® (nylidrin hydrochloride) may be of benefit in elderly patients with mild to moderate symptoms that are commonly associated with organic mental disorders. Short-term (3 months' duration) and long-term (12 months' duration) clinical studies have demonstrated a modest improvement in ability to perform general activities of daily living, self-care and in a capability for social interactions.

Although the patients appeared to be less confused, more alert, and more aware of their surroundings, an objective improvement in cognitive function has not been quantitatively determined.

In peripheral vascular disorders, ARLIDIN® (nylidrin HCl) increases walking ability and promotes healing of trophic ulcers associated with:

- arteriosclerosis obliterans
- thromboangiitis obliterans (Buerger's disease)
- diabetic vascular disease
- night leg cramp, Raynaud's phenomenon
- ischemic ulcers
- frost bite
- thrombophlebitis

ARLIDIN® has been shown to be of possible benefit in the above peripheral vascular disorders. While improvement does occur in advanced cases, experience has shown that the better the condition of the vascular bed the greater the degree of early therapeutic benefit from ARLIDIN®.

CONTRAINDICATIONS

Acute myocardial infarctions, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis.

WARNINGS and PRECAUTIONS

Medication with ARLIDIN® should not be initiated before a careful diagnosis of chronic organic brain syndrome or organic mental disorder is established since it is essential to identify the many treatable or reversible conditions or mental changes in those patients that will benefit from specific therapy.

Among the most common causes of reversible or treatable organic mental disorders are drug-induced mental changes and those due to alcohol, metabolic imbalances, nutritional deficiencies, hepatic cardiovascular and pulmonary conditions, trauma, tumors and particularly depressive and other emotional disorders.

ARLIDIN is not indicated in the management of normal aging or of patients with pre-senile dementia (Alzheimer's Disease).

The safety of use of ARLIDIN during pregnancy and lactation has not been established; therefore, it should not be administered to women of child-bearing potential, unless in the opinion of the physician, the expected benefit to the patient outweighs the potential hazard to the fetus.

In patients with cardiac disease such as tachyaffhythmias and uncompensated congestive heart failure the benefit to risk ratio should be weighed prior to therapy and reassessed periodically during treatments.

ADVERSE REACTIONS

Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension and allergic manifestations may also occur.

SYMPTOMS and TREATMENT OF OVERDOSAGE

Transient headache, flushing, shortness of breath, palpitation, or increased cardiac awareness, sinus tachycardia, transient loss of diastolic pressure and transient non-radiating chest pain.

Administer mild sedative or beta blocking drug titrated against cardiovascular response.

DOSAGE and ADMINISTRATION

The recommended dose range for relief of manifestations of peripheral vascular disorders is 12-48 mg/day given in 3-4 divided doses.

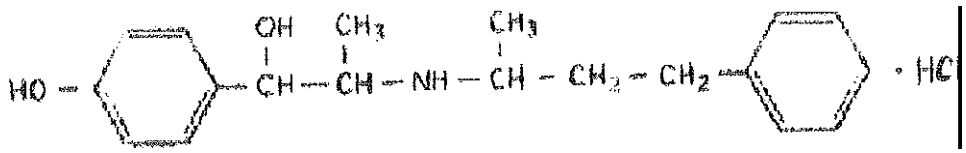
The recommended dose range for relief of selected symptoms in patients with organic mental disorders is 12-24 mg/day in 3-4 divided doses.

DOSAGE FORMS

ARLIDIN® Tablets, 6 mg: Each round, white tablet, 6.4 mm wide biconvex, 2.5 mm high, imprinted with "A" in shield, bisected one side, contains 6 mg nylidrin HCl. Available in bottles of 100, 500 and 5000 tablets.

CHEMISTRY and PHARMACOLOGY

The chemical name of nylidrin hydrochloride is: p-hydroxy-α-[l-[(l-methyl-3-phenylpropyl)amino] ethyl]benzyl alcohol hydrochloride. Its structural formula is:



Experimental studies in animals and humans show ARLIDIN® (nylidrin hydrochloride) to have a direct vasodilating action selectively upon the small arteries and arterioles of skeletal muscle, with relaxation of the muscle fibers in the media of the vessel wall. It also increases cardiac output (minute stroke volume). The effects on pulse rate and blood pressure are minimal as are untoward effects.

In a comparative study of the effect of various vasodilators on blood flow to the muscle and skin, Hensel and colleagues found that ARLIDIN 5 mg intravenously "caused the greatest increase in muscle blood flow to about 200 percent of the resting value, whereby skin blood slow remained practically unchanged",

Stein demonstrated plethysmographically in 35 patients with occlusive arterial disease that intra-arterial injection of single doses of 6 mg ARLIDIN produced a marked increase in blood flow in the calf muscle. This increase ranged from 200 to 800 percent and depended upon the vascular reserve present. The average was a 300 to 400 percent increase, which lasted for several hours. It is Stein's opinion that the absence of skin flush in the presence of a tremendous increase in blood flow to muscle indicates that the site of action is predominantly the skeletal muscle blood vessels rather than those of the skin.

Powers measured the alteration in blood following intra-arterial injection of ARLIDIN (nylidrin HCl) in 20 patients with peripheral arterial insufficiency. "A rather striking increase in blood flow in the majority of patients" occurred following injection of 5 mg in the femoral artery and "indicated that this drug will produce significant vasodilation of the muscle bed in patients with disease involving the major arteries and where intermittent claudication is the principal complaint".

De Crinis, et al. were able to demonstrate by plethysmography that ARLIDIN® increases blood flow in muscle beyond that produced physiogically by exercise. They tested the blood flow response to exercise in ten subjects (three healthy and seven with a diagnosis of occlusive vascular disease of the lower extremities) before and after intravenous administration of the drug. They found an average increase in peripheral flow of 65.5% after exercise and of 112.6% after exercise and ARLIDIN®. ARLIDIN® thus produced and additional increase in blood flow of 47.1% over exercise alone. The surface temperature was essentially the same after exercise with or without the drug. Other vasodilating drugs which are sympatholytic agents, tested in the same way, produced negligible additional rise in blood flow rate in muscle in response to exercise, while surface temperature showed a significant increase.

TOXICOLOGY

Acute Toxicity

	LD_{50}			
	Oral (mg/kg)	Subcutaneous (mg/kg)	Intraperitoneal (mg/kg)	Intravenous (mg/kg)
Mice	>250	210	-	40.0
Rats	>4800	-	380	-
Dogs	>2000	-	-	-

Chronic Toxicity

Chronic oral toxicity studies were carried out in dogs at dose levels of 0.5 g/kg daily for one month and 0.1g/kg daily for 3.5 months. All the animals remained healthy throughout the experiment and showed a normal increase in body weight. On autopsy, gross morphology was normal and histological examination revealed no evidence of tissue change. Blood counts throughout the experiment showed no appreciable change in either the red or white cell count.