The pharmacokinetics of clonidine hydrochloride are characterized by a high first-pass effect, with approximately 40% to 60% of the oral dose metabolized by the liver. Following oral administration, clonidine levels are attained in approximately 1 to 2 hours. Peak plasma concentrations are reached after 2 to 4 hours. Renal and glomerular filtration rate remains unchanged in patients with normal renal function. Acidosis may be associated with an increase in the plasma levels of clonidine. The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2 mg/ml. In patients with normal renal excretion, a further rise in the plasma levels will not enhance the antihypertensive effect.

INDICATIONS AND USAGE
Clonidine hydrochloride tablets, USP are indicated in the treatment of hypertension. Clonidine hydrochloride tablets may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS
Clonidine hydrochloride tablets should not be used in patients with known hypersensitivity to clonidine (see PRECAUTIONS).

WARNINGS
Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with clonidine hydrochloride tablets, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal syndromes.

An excessive rise in blood pressure following discontinuation of clonidine tablets can be avoided by readministration of clonidine hydrochloride or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of clonidine hydrochloride tablets.

Because children commonly have gastrointestinal illnesses that lead to vomiting, they may be prone to the manifestation of corneal lesions in rats (see CLINICAL PHARMACOLOGY).

In view of the retinal degeneration seen in rats, eye tests such as electroretinography and macular dazometry were performed in patients receiving clonidine hydrochloride. In 353 of these 308 patients, the eye examination was carried out over periods of 24 months or longer. Except for some dryness of the cornea and normal olfactory detection findings were recorded and, according to specialized techniques such as electromyography and macular dazometry, retinal function was unchanged.

In combination with amitriptyline, clonidine hydrochloride administration led to the development of normal lesions in rats within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic dietary administration of clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dose, respectively, at up to 40 or 70 mg/kg the maximum recommended daily human dose as mg/kg (9 or 6 times the MRHD on a mg/m² basis). There was no evidence of clonidine hydrochloride action on the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Pregnancy: Because animal reproduction studies are not always predictive of human response, clonidine hydrochloride tablets should be given to pregnant women only if clearly needed.

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basis) in mice and rats treated on gestation days 1 to 14 (lowest dose employed in the study was 500 mcg/kg). No safety and well-controlled studies have not been established in adequate and well-controlled trials (see Pediatric Use: clonidine has produced signs of toxicity in children. Pretreatment with naloxone has not resulted in consistent results and is not recommended as first-line therapy. Diazoxide is not likely to significantly enhance the elimination of clonidine. The largest overdose reported to date involved a 28-year-old male who ingested 100 mg of clonidine hydrochloride powder. This patient developed hypotension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment. Plasma clonidine levels were 60 ng/mL, after 1 hour, 190 ng/mL, after 1.5 hours, 310 ng/mL, after 2 hours, and 120 ng/mL, after 5.5 and 6.5 hours. In mice and rats, the oral LD50 of clonidine is 206 and 465 mg/kg, respectively.

**Dosage and Administration**

Adults: The dose of clonidine hydrochloride tablets, USP must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration.

**Initial Dose:** 0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose.

**Maintenance Dose:** Further increments of 0.1 mg per day may be made at weekly intervals if necessary until the desired response is achieved. Taking only the largest portion of the oral dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day given in divided doses.

Studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed.

**Renal Impairment:** Patients with renal impairment may benefit from a lower initial dose. Patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis. For questions regarding this product call Actavis at 1-800-432-8534.

**How Supplied**

Clonidine hydrochloride tablets, USP are supplied as follows:

0.1 mg — Each orange, round tablet imprinted with 1-79 on one side and bisect on the other side contains 0.1 mg of clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2127-10) and 500 (NDC 0228-2127-50).

0.2 mg — Each orange, round tablet imprinted with 17 on one side and bisect on the other side contains 0.2 mg of clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2128-10) and 500 (NDC 0228-2128-50).

0.3 mg — Each orange, round tablet imprinted with 1 on one side and 128 and bisect on the other side contains 0.3 mg of clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2129-10) and 500 (NDC 0228-2129-50).

Clonidine hydrochloride tablets, USP 0.1 mg are distributed by Major Pharmaceuticals in cartons of 100 tablets, NDC 0004-5561-61.

Clonidine hydrochloride tablets, USP 0.2 mg are distributed by Major Pharmaceuticals in cartons of 100 tablets, NDC 0004-5562-61.

Clonidine hydrochloride tablets, USP 0.3 mg are distributed by Major Pharmaceuticals in cartons of 100 tablets, NDC 0004-5563-61.

Clonidine hydrochloride tablets, USP 0.4 mg are distributed by Major Pharmaceuticals in cartons of 100 tablets, NDC 0004-5564-61.

Dispense in a tight, light-resistant container as directed by the USP. Store at 25°C (77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].