MINOXIDIL

Category

Antihypertensive.

Indications

Accepted

Hypertension (treatment) Minoxidil is indicated for treatment of hypertension .

Because of its serious side effects, minoxidil is not considered to be a primary agent in the treatment of essential hypertension. It is recommended for use only in patients with symptomatic or organ-damaging hypertension not responsive to other treatment. 1

Unaccepted

Use of extemporaneous topical preparations from minoxidil oral tablets is not recommended for treatment of male pattern baldness because there is lack of data on the best formulation and the risks associated with possible systemic absorption. A topical product is commercially available for this indication.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾209.25

pKa¾Approximately 4.6

Mechanism of action/Effect:

The exact cellular mechanism of antihypertensive action is unknown. The predominant effect of minoxidil is direct vasodilation of arterioles with little effect on veins. It reduces peripheral resistance and causes a reflex increase in heart rate and cardiac output.

Absorption:

At least 90% absorbed from the gastrointestinal tract.

Biotransformation:

Hepatic, at least 90%; metabolites have much less pharmacologic activity than minoxidil.

Half-life:

Drug and metabolites¾4.2 hours 1, 2 ; not altered in impaired renal function.

Onset of action:

30 minutes.

Time to peak concentration:

1 hour.

Time to peak effect:

Single dose¾2 to 3 hours.

Multiple doses¾Maximum blood pressure response with continued use usually occurs within 3 to 7 days (patients receiving the largest doses respond in the shortest period of time and vice versa).

Duration of action:

Usually 24 to 48 hours; up to 75 hours in some patients.

Elimination:

Fecal¾3% (may be increased to up to 20% in severe renal function impairment).

Renal¾97%, mostly as metabolites.

In dialysis¾Removable by hemodialysis; however, this does not rapidly reverse the pharmacologic effect 7.

Precautions to Consider

Carcinogenicity

Twenty-two-month studies in rats at doses 15 times the human dose revealed no evidence of tumorigenicity. 1

Mutagenicity

In Ames test, no evidence of mutagenicity was found. 1

Pregnancy/Reproduction

Fertility¾A reduction in conception rate occurred in rats receiving minoxidil at doses 5 times the human dose. 1

Pregnancy¾Minoxidil crosses the placenta. Studies in humans have not been done. However, hypertrichosis has been reported in newborns following maternal minoxidil administration. 3, 4

Studies in rats and rabbits did not reveal teratogenic effects; however, there was an increased incidence of fetal resorptions in rabbits given minoxidil at 5 times the human dose.

FDA Pregnancy Category C.

Breast-feeding

Minoxidil passes into breast milk. However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of minoxidil have not been performed in the pediatric population. However, pediatrics-specific problems that would limit the usefulness of this medication in children are not expected.

Geriatrics

Although appropriate studies on the relationship of age to the effects of minoxidil have not been performed in the geriatric population, the elderly may be more sensitive to the hypotensive effects. In addition, the risk of minoxidil-induced hypothermia may be increased in elderly patients. Elderly patients are also more likely to have age-related renal function impairment, which may require reduction of dosage in patients receiving minoxidil.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

>> Antihypertensives, potent parenteral, such as diazoxide or nitroprusside or

>> Guanethidine or

>> Nitrates

(concurrent use with minoxidil may result in a severe, additive hypotensive effect; patients should be continuously observed for excessive fall in blood pressure for several hours after concurrent administration of potent peripheral antihypertensives or nitrates; concurrent use with guanethidine is not recommended)

Anti-inflammatory drugs, nonsteroidal (NSAIDs), especially indomethacin

(may reduce antihypertensive effects of minoxidil; indomethacin, and possibly other NSAIDs, may antagonize the antihypertensive effect by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention; the patient should be carefully monitored to confirm that the desired effect is being obtained)

Hypotension-producing medications, other (see Appendix II)

(hypotensive effects may be potentiated when these medications are used concurrently with minoxidil)

(although some antihypertensive and/or diuretic combinations are used for therapeutic advantage, dosage adjustments may be necessary during concurrent use)

Sympathomimetics

(may reduce antihypertensive effects of minoxidil; the patient should be carefully monitored to confirm that the desired effect is being obtained)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Alkaline phosphatase concentrations, serum and

Plasma renin activity (PRA) and

Sodium concentrations, serum

(may be increased)

Blood urea nitrogen (BUN) and

Creatinine

(serum concentrations may be increased initially, but decline to pretreatment levels with continued treatment)

Erythrocyte count and

Hematocrit and

Hemoglobin concentrations

(may be decreased as a result of hemodilution; usually recover to pretreatment levels with continued treatment)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

Cerebrovascular disease or accident or

Myocardial infarction

(a reduction in arterial pressure caused by minoxidil may further limit blood flow to the ischemic area)

>> Congestive heart failure not due to hypertension

(may be exacerbated secondary to fluid retention caused by minoxidil)

>> Coronary insufficiency, including angina pectoris

(may be exacerbated)

>> Pericardial effusion

(minoxidil may aggravate this condition)

>> Pheochromocytoma

(use may stimulate release of catecholamines from the tumor)

>> Renal function impairment

(reduced elimination; lower doses may be required)

Sensitivity to minoxidil 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

>> Blood pressure measurements

(recommended at periodic intervals in patients being treated for hypertension; selected patients may be trained to perform blood pressure measurements at home and report the results at regular physician visits)

>> Weight measurements

(daily weight measurements by the patient are recommended to detect excessive sodium and water retention)

Side/Adverse Effects

Note: Minoxidil has been shown to cause severe myocardial toxicity in dogs. However, this effect has not been observed in other animals or in humans at this time, although nonspecific electrocardiogram (ECG) changes are commonly seen, pericardial effusion (sometimes progressing to cardiac tamponade) occurs in about 3% of patients, and pericarditis has been reported.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

Reflex sympathetic activation (fast or irregular heartbeat; flushing or redness of skin); sodium and water retention (bloating; swelling of feet or lower legs; rapid weight gain of more than 5 pounds [2 kg] in adults or 2 pounds [1 kg] in children)

Incidence less frequent

Angina, new or exacerbated, or pericarditis 1, 5, 6 (chest pain)

Incidence rare

Allergic reaction or Stevens-Johnson syndrome 1, 8 (skin rash and itching)

With long-term use

Paresthesia (numbness or tingling of hands, feet, or face); pericardial effusion 1 or pulmonary hypertension (shortness of breath)

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent¾occurs in most patientsHypertrichosis (excessive hair growth, usually on face, arms, and back)

Note: Hypertrichosis usually develops within 3 to 6 weeks after initiation of minoxidil therapy, and return to pretreatment appearance occurs approximately 1 to 6 months after the medication is

withdrawn. The increased hair growth may be extensive and may be especially disturbing to women and children; various depilatory methods may help.

Incidence less frequent or rare

Breast tenderness in males and females; vasodilation (headache)

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

Administration of intravenous sodium chloride injection is recommended to maintain blood pressure and facilitate urine formation.

Sympathomimetics such as norepinephrine or epinephrine should be avoided because of the risk of excessive cardiac stimulation.

Hypotension may be treated with phenylephrine, vasopressin, or dopamine, but they are recommended only if lack of perfusion of a vital organ occurs.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Minoxidil (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to minoxidil

Pregnancy¾Decreased conception and increased resorption in animals; hypertrichosis reported in newborns

Breast-feeding¾Passes into breast milk

Other medications, especially guanethidine or nitrates

Other medical problems, especially congestive heart failure, coronary insufficiency, pericardial effusion, pheochromocytoma, or renal function impairment

Proper use of this medication

Possible need for control of weight and diet, especially sodium intake

>> Patient may not experience symptoms of hypertension; importance of taking medication even if feeling well

>> Does not cure, but helps control hypertension; possible need for lifelong therapy; serious consequences of untreated hypertension

Compliance with therapy; taking medication at the same time(s) each day to maintain the therapeutic effect

Caution in taking combination therapy; taking each drug at the right time

>> Proper dosing

Missed dose: Taking as soon as remembered if within a few hours; not taking if forgotten until next day; not doubling doses

>> Proper storage

Precautions while using this medication

Making regular visits to physician to check progress

>> Checking resting pulse as directed; checking with physician if an increase of 20 or more beats per minute above normal occurs

>> Checking weight daily; weight gain of 2 to 3 lb (approximately 1 kg) in adults is normal and is usually lost with continued treatment; checking with physician if rapid weight gain of more than 5 lb (2 lb in children) or signs of fluid retention occur

>> Not taking other medications, especially nonprescription sympathomimetics, unless discussed with physician

Side/adverse effects

Probability of hypertrichosis, which is reversible when medication is withdrawn

Signs of potential side effects, especially sodium and water retention, reflex sympathetic activation, angina, pericarditis, allergic reaction, Stevens-Johnson syndrome, paresthesia, and pulmonary hypertension

General Dosing Information

Sodium and water retention occurs rapidly in almost all patients receiving minoxidil and is difficult to control. Concomitant use of a diuretic (usually a loop diuretic) is recommended to prevent serious fluid accumulation and possible development of tolerance due to expansion of plasma volume.

Reflex tachycardia also occurs very commonly and may be less pronounced if a beta-adrenergic blocking agent or other sympathetic nervous system suppressant is used concurrently. The usual dose of beta-adrenergic blocker recommended is the equivalent of 80 to 160 mg of propranolol a day in divided doses. If beta-adrenergic blocking agents cannot be used, methyldopa in a dose of 250 to 750 mg twice a day may be substituted. Some investigators have used clonidine in a dose of 100 to 200 mcg (0.1 to 0.2 mg) twice a day.

If pericardial effusion occurs and does not respond to therapeutic measures, it is recommended that minoxidil therapy be withdrawn.

Because a few cases of rebound hypertension have been reported following abrupt withdrawal of minoxidil, caution is recommended when discontinuing the medication.

Oral Dosage Forms

MINOXIDIL TABLETS USP

Usual adult and adolescent dose

Antihypertensive¾

Initial: Oral, 5 mg a day as a single dose 1 or as two divided doses 2 , the dosage being adjusted in 100% increments as required (i.e., up to 10, 20, 40 mg, etc.).

Maintenance: Oral, 10 to 40 mg a day, as a single dose or in divided daily doses 1, 2.

Note: It is recommended that an interval of at least three days be allowed between each dosage adjustment, in order for the full effect of each dose to be obtained. In some patients, dosage adjustment may be made every six hours with careful monitoring.

Geriatric patients may be more sensitive to effects of the usual adult dose.

Usual adult prescribing limits

100 mg a day.

Usual pediatric dose

Antihypertensive¾

Children up to 12 years of age¾

Initial¾Oral, 200 mcg (0.2 mg) per kg of body weight a day as a single dose 1 or as two divided doses 2 , the dosage being adjusted as required (i.e., in increments of 100, 150, 200 mcg per kg of body weight, etc.), up to 50 mg a day.

Maintenance¾Oral, 250 mcg (0.25 mg) to 1 mg per kg of body weight a day, as a single dose or in divided daily doses, up to 50 mg a day.

Children over 12 years of age¾

See Usual adult and adolescent dose.

Note: It is recommended that an interval of at least three days be allowed between each dosage adjustment, in order for the full effect of each dose to be obtained. When more rapid control of blood pressure is required, dosage adjustment may be made every six hours with careful monitoring.

Strength(s) usually available

U.S.¾2.5 mg (Rx)[Loniten (scored)] [Generic] (scored)

10 mg (Rx)[Loniten (scored)] [Generic] (scored)

Canada¾2.5 mg (Rx)[Loniten (scored)]

10 mg (Rx)[Loniten (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F) unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Do not take other medicines without your doctor's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.