PRODUCT MONOGRAPH

PrMINT-CLONIDINE

Clonidine Hydrochloride Tablets

0.025 mg

USP

Vascular Stabilizer for the Treatment of Menopausal Flushing

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Date of Preparation:
January 24, 2023

Submission Control No: 270645

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Clonidine Hydrochloride Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Nonmedicinal Ingredients
Oral	Tablet / 0.025 mg	**Core:** Colloidal silicon dioxide, Dicalcium phosphate, Lactose monohydrate, Magnesium stearate, Pregelatinized maize starch **Coating:** FD&C Blue #2 Hypromellose, Polyethylene Glycol, Polyvinyl alcohol, Talc, Titanium Dioxide

INDICATIONS AND CLINICAL USE
MINT-CLONIDINE (clonidine hydrochloride) is indicated for the relief of menopausal flushing in patients for whom hormonal replacement therapy is either unnecessary or not desirable.

Pediatrics (< 18 years of age):
Safety and effectiveness in children has not been established.

CONTRAINDICATIONS
MINT-CLONIDINE (clonidine hydrochloride) is contraindicated in patients with the following:

- know hypersensitivity to the active substance or to any of the ingredients of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- severe bradyarrhythmia resulting from either sick sinus syndrome or atrioventricular block of 2nd or 3rd degree; patients with sinus node function impairment.
- rare hereditary conditions that may be incompatible with an excipient of the product (see DOSAGE FORMS, COMPOSITION AND PACKAGING sections).
  This product contains 235.1 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

WARNINGS AND PRECAUTIONS

General

An abrupt withdrawal of higher doses of clonidine hydrochloride is followed in some cases by an excess of circulating catecholamines. Therefore, caution should be exercised in concomitant use of drugs which affect the metabolism, tissue uptake or pressor effects of these amines (monoamine oxidase inhibitors, tricyclic antidepressants and beta-blocking agents) (see DRUG INTERACTIONS section).

MINT-CLONIDINE (clonidine hydrochloride 0.025 mg) should not be confused with higher strength dosage forms containing the same active ingredient (clonidine hydrochloride 0.1 mg or 0.2 mg) used for treating hypertension. Caution should however be exercised in patients receiving antihypertensive therapy because of the possibility of an additive effect.

Note: MINT-CLONIDINE is only available in a 0.025 mg strength tablet.

Patients who engage in potentially hazardous activities such as operating machinery or driving should be warned of the possible sedative effect of clonidine hydrochloride (see WARNINGS AND PRECAUTIONS: Effects on ability to drive and use machines**)**. Caution should be exercised in the concomitant administration of sedatives, tranquilizing drugs or alcohol (see DRUG INTERACTIONS).

Patients should be instructed not to discontinue therapy without consulting their physician (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment section).

Carcinogenesis and Mutagenesis

See the TOXICOLOGY section.

Cardiovascular

Blood Pressure

Clonidine hydrochloride can have a hypotensive effect especially in high doses. In patients whose blood pressure decreases to an intolerable extent when taking MINT- CLONIDINE, treatment should be discontinued.

An excessive rise in blood pressure following discontinuation of MINT-CLONIDINE therapy can be reversed by intravenous phentolamine.

Because it can lower blood pressure at high doses, MINT-CLONIDINE (clonidine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebral vascular disease, or chronic renal failure. MINT-CLONIDINE should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus

rhythm, with disorders of cerebral or peripheral perfusion, polyneuropathy, and constipation, patients with heart failure or severe coronary heart disease.

Heart Rate

Depending on the dose given, MINT-CLONIDINE can lower the heart and pulse rate. In patients with diseases affecting the rhythmic and atrioventricular conduction system of the heart, arrhythmias have been observed after high doses.

Heart Disease

Patients with heart failure or severe coronary disease should be monitored particularly carefully when using MINT-CLONIDINE.

Other

A few instances of a condition resembling Raynaud's phenomenon have been reported with the higher doses of clonidine as used in the therapy of hypertension. Caution should be observed if patients with Raynaud's disease or thromboangiitis obliterans are to be treated with MINT-CLONIDINE

Ophthalmologic

In several studies clonidine hydrochloride produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for six months or longer (see TOXICOLOGY). In view of this retinal degeneration, eye examinations were performed in 908 hypertensive patients prior to the start of clonidine hydrochloride therapy, who were then examined periodically thereafter. In 353 of these 908 patients, examinations were performed for periods of 24 months or longer. Except for the dryness of the eyes, no drug-related abnormal ophthalmologic findings were recorded and clonidine hydrochloride did not alter retinal function as shown by specialized tests such as the electroretinogram and macular dazzle.

Patients who wear contact lenses should be warned that treatment with MINT-CLONIDINE may cause decreased lacrimation.

Psychiatric

Patients with a known history of depression should be carefully supervised while under treatment with clonidine as there have been occasional reports of further depressive episodes occurring in such patients.

Renal

Clonidine and its metabolites are extensively excreted with urine. As a result, MINT-CLONIDINE should be used with caution in patients with renal insufficiency. Careful monitoring of blood pressure is required.

As with any drug excreted primarily in the urine, smaller doses of the drug are often effective in treating patients with a degree of renal failure. In patients exhibiting renal failure or insufficiency, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

Sexual Function/Reproduction

No clinical studies on the effect on human fertility have been conducted with clonidine. Non-clinical studies with clonidine indicate that it adversely affects fertility in female rats (see TOXICOLOGY).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Thus, use of clonidine hydrochloride in pregnancy is not recommended. In case of accidental use of clonidine hydrochloride in pregnancy, careful monitoring of mother and child is recommended. There is no adequate experience regarding the long-term effects of prenatal exposure. Clonidine passes the placental barrier and may lower the heart rate of the fetus. Also in post-partum a transient rise in blood pressure in the newborn cannot be excluded.

Non-clinical studies showed clonidine hydrochloride to have adverse effects with respect to reproductive toxicity at doses below the clinically administered dose (see TOXICOLOGY).

Nursing Women: Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of MINT-CLONIDINE is therefore not recommended during breast feeding.

Pediatrics (<18 years of age): Safety and effectiveness in children has not been established.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with MINT-CLONIDINE. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Most adverse reactions associated with the use of clonidine hydrochloride are mild and diminish with continued therapy.

Accumulated clinical and post-marketing data indicate provides some insight into adverse reactions. The information from this section is based on 22 clinical studies, which were published between 1968 and 1985. The studies comprised of 640 patients, which have been treated with clonidine hydrochloride. The following lists of adverse reactions have been noted with the use of clonidine hydrochloride.

Endocrine disorders:
gynaecomastia

Psychiatric disorders:
confusional state, delusional perception, depression, hallucination, libido decreased, nightmare, sleep disorder

Nervous system disorders:
dizziness, headache, paraesthesia, sedation
Eye disorder:
accommodation disorder, lacrimation decreased

Cardiac disorders:
atrioventricular block, bradyarrhythmia, sinus bradycardia

Vascular disorders:
orthostatic hypotension, Raynaud's phenomenon, reduction in blood pressure

Respiratory, thoracic and mediastinal disorders:
nasal dryness

Gastrointestinal disorders:
colonic pseudo-obstruction, constipation, dry mouth, nausea, salivary gland pain, vomiting, cramps, accelerated rate of dental caries

Skin and subcutaneous tissue disorders:
Alopecia, pruritus, rash, urticaria

Reproductive system and breast disorders:
erectile dysfunction

General disorders and administration site conditions:
fatigue, malaise, drowsiness, muscle or joint pain

Investigations:
blood glucose increased

DRUG INTERACTIONS

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Proper name	References	Effect	Clinical comment
Other anti-hypertensive agents such as diuretics, vasodilators, β blockers, calcium antagonists and ACE-inhibitors, but not α_1-blocking agents		The reduction in blood pressure induced by clonidine can be further potentiated by concurrent administration.	
B-blockers and/or cardiac glycosides		Concomitant use can further lower heart rate (bradycardia) or cause dysrhythmia (atrioventricular block) in isolated cases.	
Beta-receptor blocker		It cannot be ruled out that concomitant administration will cause or potentiate peripheral vascular disorders.	
Tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties		The antihypertensive effect of clonidine may be reduced or abolished and orthostatic regulation disturbances may be provoked or aggravated by concomitant administration. Amitriptyline in combination with clonidine hydrochloride enhances the manifestation of corneal lesions in rats (see TOXICOLOGY).	If clonidine hydrochloride and tricyclic antidepressants are administered as concurrent therapy, an increase in the dosage of MINT-CLONIDINE may be necessary.
Substances with alpha$_2$ receptor blocking properties such as phentolamine		May abolish the alpha$_2$-receptor mediated effects of clonidine in a dose-dependent manner.	
Sympathomimetic amines, indomethacin and possibly other non-steroidal anti-inflammatory agents		May reduce the antihypertensive effects of clonidine hydrochloride. Substances which raise blood pressure or induce a Na^+ and water retaining effect such as non steroidal anti-inflammatory agents can reduce the therapeutic effect of clonidine.	The patient should be carefully monitored to confirm that the desired effect is being obtained.
Alcohol, barbiturates or other sedatives.		Clonidine hydrochloride may enhance the CNS-depressive effects	
Drugs which affect the metabolism, tissue uptake or pressor effects of catecholamines (monoamine oxidase (MAO) inhibitors, tricyclic antidepressants and beta blocking agents, respectively).		Withdrawal of clonidine hydrochloride may result in an excess of circulating catecholamines (see WARNINGS AND PRECAUTIONS).	Caution should be exercised in concomitant use of these drugs.
Methylphenidate	Popper CW, 1995 (22) (See REFERENCES)	The concomitant use with clonidine has resulted in serious adverse reactions, including death, in children with attention-deficit/hyperactivity (ADHD).	

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Test Interactions
In rare cases, an increase in blood glucose has occurred in clinical studies.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dose for the treatment of menopausal flushing is 0.05 mg of MINT-CLONIDINE (clonidine hydrochloride) twice daily. If after two to four weeks there has been no remission, the treatment should be discontinued and the patient reassessed.

Attempts should be made to discontinue treatment at three to six month intervals for patient re-evaluation of menopausal symptoms.

Following sudden discontinuation of clonidine hydrochloride after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with MINT-CLONIDINE, the physician should reduce the dose gradually over 2-4 days.

Missed Dose
If a dose of MINT-CLONIDINE is missed, patients should take the dose as soon as possible and then return to their normal schedule.

Administration
The tablets should be swallowed whole with water.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The signs and symptoms of clonidine hydrochloride overdosage are due to generalized sympathetic depression and include pupillary constriction, hypotension, hypothermia, bradycardia, lethargy, irritability, weakness, somnolence including coma, diminished or absent reflexes, vomiting and hypoventilation. With large overdoses, reversible cardiac conduction defects or arrhythmias, coma, respiratory depression including apnea, seizures and transient hypertension have been reported.

In a patient who ingested 100 mg clonidine hydrochloride, plasma clonidine levels were 60 ng/mL (one hour), 190 ng/mL (1.5 hours), 370 ng/mL (two hours) and 120 ng/mL (5.5 and 6.5 hours). This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MINT-CLONIDINE (clonidine hydrochloride) reduces the response of peripheral vessels to either vasoconstrictor or vasodilator stimuli. Clonidine hydrochloride, the active ingredient, is an α-adrenergic agonist which also has some α-adrenergic antagonist effects.

Clonidine hydrochloride therapy has been shown to reduce the frequency, severity, and duration of flushing attacks associated with the menopausal syndrome. There is a gradual onset of therapeutic response, and a gradual return of symptoms on interruption of treatment.

MINT-CLONIDINE will not correct or relieve other menopausal changes that are due to hormonal deficiencies.

Clonidine stimulates alpha-adrenoreceptors in the brain stem, resulting in reduced sympathetic outflow from the central nervous system and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged.

Acute studies with clonidine hydrochloride in humans have demonstrated a moderate reduction (15%-20%) of cardiac output in the supine position with no change in the peripheral resistance, at a 45° tilt there is a smaller reduction in cardiac output and a decrease in peripheral resistance. During long-term therapy, cardiac output tends to return to controlled values, while peripheral resistance remains decreased.

Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines, but the exact relationship of these pharmacologic actions to the antihypertensive effect has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

Pharmacodynamics

Clonidine hydrochloride acts relatively rapidly. The patient's blood pressure declines within 30 to 60 minutes after an oral dose, the maximum decrease occurring within 2 to 4 hours.

In humans, the blood pressure reduction due to higher doses of clonidine does not cause significant alterations in renal blood flow in the supine position. In the erect position, a consistent decrease in renal vascular resistance is seen.

Absorption: The plasma level of clonidine hydrochloride peaks in approximately 3 to 5 hours. In humans, a significant plasma level (0.20 mcg% of clonidine) can be detected one hour after oral administration of a single dose of 390 mcg.

Distribution: Clonidine is 30-40% bound to plasma proteins**.**

Metabolism: About 50% of the absorbed dose is metabolized in the liver. Four different metabolites have been detected in humans.

Excretion: Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. Clonidine is excreted in human milk (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women). However, there is insufficient information on the effect of newborns.

The terminal elimination half-life ranges from 5 to 25.5 hours, but the half-life increases up to 41 hours in patients with severe impairment of renal function. In humans, 65% of the orally administered drug is excreted in the urine, and an estimated 22% in the faeces.

STORAGE AND STABILITY

MINT-CLONIDINE tablets should be stored between 15°C -30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

0.025 mg tablet: Round, blue colored, biconvex coated tablet, debossed “0.025” on one side and plain on the other side.

Composition

The MINT-CLONIDINE (clonidine hydrochloride) tablet core contains clonidine hydrochloride and the following non-medicinal ingredients: colloidal silicon dioxide, dicalcium phosphate, lactose monohydrate, magnesium stearate, pregelatinized maize starch.

The MINT-CLONIDINE tablet coating contains: FD&C Blue #2, hypromellose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

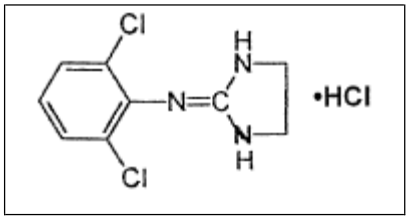
Packaging

MINT-CLONIDINE 0.025 mg tablets are supplied in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	clonidine hydrochloride
Chemical Name	2-[(2,6-Dichlorophenyl) imino]imidazolidine monohydrochloride
Structural Formula	
Molecular Formula	$C_9H_9N_3Cl_2$•HCl
Molecular Mass	266.5 g/mol
Physicochemical properties:	Clonidine hydrochloride occurs as white or almost white crystalline powder. It is soluble in water and ethanol; slightly soluble in chloroform. The pH of a 5% aqueous solution lies between 3.5 and 5.5.

CLINICAL STUDIES

Comparative Bioavailability Study

A two-way, single dose (2 x 0.025 mg) crossover comparative bioavailability study of MINT-CLONIDINE (MINT Pharmaceuticals Inc.) and TEVA-CLONIDINE (Teva Canada Limited, Canada) was conducted in healthy subjects under fasting conditions. A summary of the bioavailability data from the 27 subjects who completed the study is presented in following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clonidine (2 x 0.025 mg) Geometric Mean Arithmetic Mean (CV %)				
Pharmacokinetic Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·hr/mL)	3082.61 3151.30 (21.25)	3317.73 3385.87 (20.48)	92.9	89.1 – 96.8
AUC_I (pg·hr/mL)	3381.28 3454.51 (20.98)	3637.47 3708.70 (19.88)	92.9	89.1 - 96.8
C_{max} (pg/mL)	233.45 238.11 (22.08)	240.24 244.82 (20.64)	97.2	93.1 - 101.4
T_{max}[3] (h)	1.33 (0.50 - 4.50)	1.33 (0.75 - 4.00)		
$T½$[4] (h)	11.39 (20.86)	11.91 (20.36)		

[1]MINT-CLONIDINE (clonidine hydrochloride) tablet, 0.025 mg (MINT Pharmaceuticals Inc.)
[2]TEVA-CLONIDINE (clonidine hydrochloride) tablet, 0.025 mg (Teva Canada Limited)
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (CV %) only

DETAILED PHARMACOLOGY

Pharmacokinetics

Clonidine is well absorbed from the intestine in all species examined. In the dog, plasma levels can be detected one hour after administration of an oral dose of 0.52 mg/kg, and maximum plasma levels are reached after 4-8 hours. In man, a significant plasma level (0.20 mcg% of clonidine) can be detected one hour after oral administration of a single dose of 390 mcg. Since clonidine is approximately 50% bound, this reflects an actual free plasma level. Peak plasma levels in man and monkey occur after three hours and decline with a half-life of twenty hours. Elimination decreases after twenty-four hours and is completed only after five days.

In rats, clonidine hydrochloride tissue levels are distinctly above blood levels. They show similar distribution patterns over heart, liver, lung, spleen, testes, brain, adrenal gland, fat and muscle after either oral or i.v. administration. The highest concentration of clonidine after oral administration is found in the kidneys and the gastrointestinal tract, but only very small amounts can be detected in these organs forty-eight hours after administration. There is a high concentration of clonidine in the lacrimal and parotid glands (40 times higher than the blood level).

The cerebrospinal fluid contains only half the plasma concentration of clonidine, which might be interpreted as an expression of affinity for brain tissue. The overall brain distribution suggests a greater affinity for noradrenergic than for other aminergic cell systems.

An enterohepatic circulation of clonidine has been described in the rat. Up to 24% of an oral dose is excreted in the bile, within the first 24-48 hours.

A large proportion (90- 95%) of the given dose is metabolized in dogs and monkeys, whereas in humans clonidine is less extensively metabolized. In dogs, after 48 hours up to 80% of the administered radioactive clonidine is excreted in the urine, and up to 18% in the feces. In man, 65% of the orally administered drug is excreted in the urine and an estimated 22% in the feces. Fifty-eight percent of the activity in human urine at 24 hours, and 44% at 48 hours is unchanged clonidine. Four different metabolites have been detected in man.

Effects on the Cardiovascular System

Clonidine has two opposing actions on the cardiovascular system. As an alpha-sympathomimetic it constricts blood vessels but, as it seems devoid of beta-stimulant action, it does not directly influence the heart. The very potent inhibitory action on central spontaneous sympathetic activity tends to reduce the peripheral resistance and to decrease cardiac output. In addition, a vagal component appears to be involved, since phentolamine or reserpine abolish the effect on blood pressure but only decrease the bradycardia produced by clonidine, while atropine decreases the hypotension and bradycardia.

Clonidine has neither a ganglionic nor a postganglionic blocking action; it is free of alpha- and beta-adrenergic blocking actions; it does not act on vagal receptors, and it does not interfere with the catecholamine content of the various tissues.

Intravenous doses (1-100 mcg/kg) of clonidine given to animals of different species, either intact or in various experimental preparations, exert a biphasic cardiovascular effect: (a) an initial very brief rise of the blood pressure is followed by (b) a sustained fall.

a) The brief vasopressor effect shows the following characteristics: (1) it is not prevented by pre-treatment with reserpine; (2) it is abolished by pretreatment with phentolamine; (3) it is reduced by cocaine; (4) it is still elicited in the spinal, decerebrated, decapitated, pithed, immunosympathectomized, bivagotomized, stellate ganglionectomized and debuffered animal; and (5) it is accompanied by bradycardia.

In addition clonidine causes direct vasoconstriction in isolated organs. In experiments with isolated smooth muscles of rabbits (non-pregnant uterus, small intestine and blood vessels of the ear), clonidine appears to compete with adrenaline and causes an adrenaline-like effect.

Contrary to the initial vasopressor effect of guanethidine and bretylium, clonidine does not interfere with the synthesis, storage, or release of catecholamines from the nerve endings. Clonidine is less depressant than guanethidine upon reflex blood pressure responses, as shown by the conservation of the normal diving reflex in ducks and by the absence of effect on the blood pressure response to vertical tilting in dogs. However, clonidine markedly enhances the pressure-induced reflex bradycardia in dogs (total heart-lung bypass); this effect is abolished by stellate ganglionectomy and bivagotomy.

Bradycardia is seen with 5 mcg/kg i.v. in experimental animals, but total denervation of the heart abolishes any bradycardiac response to i.v. doses as high as 1 mg/kg. In very high doses it has been shown, however, that clonidine is depressant directly upon the myocardium.

b) The long-lasting, slow-recovering depressor phase of clonidine is clearly dose-dependent and shows the following characteristics:

    (1) it is inhibited by pretreatment with reserpine or phentolamine; (2) it is absent in the spinal, pithed or decapitated animal; (3) it is elicited by injection of minute quantities (even 1/100 of the intravenous dose) administered directly into the central nervous system (intracisternal, intrahypothalamic or intraventricular injection, or infusion into the vertebral arteries) and (4) it is also accompanied by bradycardia which persists throughout the entire blood pressure response to clonidine.

Clonidine reduces the cardiac output in dogs and rabbits. Apparently, this is not due to a direct negative inotropic effect upon the cardiac muscle or to a local action on the pacemaker region, nor does it arise as a reflex response to a change in blood pressure. It is apparently due to a reduction in the sympathetic drive to the heart or to the systemic venodilatation caused by the drug. No change is seen in this cardiac response after vagotomy.

Clonidine decreases the neuronal traffic in the sympathetic nervous system or at least changes the pattern of sympathetic discharges, inhibiting centrally the bulbar sympathetic cardioaccelerator and vasoconstrictor mechanisms. In different animal species the impulse traffic in the renal, phrenic, cervical, splanchnic, and cardiac sympathetic nerves (pre- or postganglionic) rapidly decreases after clonidine and finally disappears. Clonidine does not reduce the discharges in all the sympathetic nerves to the same extent, the cardiac nerve being less affected. This effect is dose-dependent, lasts as long as the hypotension and the bradycardia and is not influenced by vagotomy nor by suppression of afferent input from the peripheral chemo- and baroreceptors.

The depression of the sympathetic activity is more effective on the spontaneous discharges than on reflexly or centrally evoked discharges, especially if submaximal or supramaximal stimulation at low frequencies is used. An adrenergic block is not the reason for the decrease in

the sympathetic tone since low doses of clonidine potentiate and prolong the blood pressure effect of adrenaline and prolong the responses to noradrenaline.

The biphasic change in arterial blood pressure is accompanied by a corresponding sharp increase and then a fall in total peripheral resistance. The significant reduction in the total peripheral resistance obtained in unanaesthetized rabbits by single intravenous injections of clonidine is unaffected even when the effects of the autonomic nervous system are blocked by pretreatment with phenoxybenzamine, propranolol and atropine. This indicates that clonidine may have a direct peripheral vasodilator action in addition to its effect on the CNS and its peripheral sympathomimetic effect, especially when the level of resting sympathetic activity is low. In dogs there is a decreased skin and skeletal muscle blood flow during the transient pressor phase, but the coronary blood flow is increased, indicating either a lesser degree of vasoconstriction relative to that in other vascular fields, or vasodilatation.

The depressor phase usually shows an increase in the circulatory capacity. There is a corresponding change in the regional distribution of blood in the peripheral circulation; the vascular resistance in the cutaneous and skeletal beds decreases, whereas the cerebral, pulmonary renal and splanchnic vascular fields show variable responses. A fall in the calculated coronary vascular resistance has been demonstrated in the dog heart-lung bypass preparation with separate coronary and systemic perfused circulation, even when the heart rate was maintained constant.

Effects on Vascular Reactivity
Administration of oral clonidine to cats at a dose of 10 mcg/kg/day for 4 weeks or 20 mcg/kg/day for seven days resulted in a reduction in vascular response to either vasoconstrictor or vasodilator stimuli. The vasoactive drugs administered under general anesthesia were epinephrine, norepinephrine, isoprenaline and angiotensin.

Reduced vascular reactivity to angiotensin, norepinephrine and vasopresin administered intravenously was observed in conscious rats, These effects were also seen after single intramuscular doses of 1, 3, or 10 mcg/kg of clonidine either before or after ganglion blockade as well as after seven days of intramuscular administration of 20 mcg/kg of clonidine.

Effects on the Kidney, Renal Hemodynamics and Sodium Balance
In acute studies clonidine given intravenously or by infusion into the renal artery diminishes the renal blood flow and reduces the excretion of sodium in dogs. However, the intravenous or intraperitoneal administration of clonidine to rats enhances the diuresis and produces a dose-dependent increase in the excretion of inorganic ions, their relative composition being quite uniform.

In man, the blood pressure reduction due to higher doses of clonidine does not cause significant alterations in renal blood flow in the supine position. In the erect position, a consistent decrease in renal vascular resistance is seen.

In animals, acute administration of the drug causes a dose-related increase in renal vascular resistance without any change in glomerular filtration rate. There is correlation between these effects and increased tubular reabsorption of sodium.

Clinically there may be some sodium retention and slight weight gain during the initial three to four days of clonidine hydrochloride therapy for hypertension. Thereafter, the sodium is re-excreted and weight goes down during continued administration of the drug. These transient changes in sodium balance are rarely of clinical significance and are not seen at all if clonidine is given concomitantly with a diuretic.

Effects on the Central Nervous System
In acute experiments a dose-dependent sedative action has been demonstrated in cats and dogs receiving i.v. clonidine. In rats there is a reduction of exploratory behaviour and inhibition of pain-induced aggression in doses smaller than or equal to those effective in producing hypotension.

Mice have shown exophthalmos, horripilation and intense tremors at 1-5 mg/kg and marked aggressivity at 10 mg/kg, followed by sedation and reduction of spontaneous mobility. The conditioned avoidance behaviour of guinea pigs and rats is inhibited by clonidine, and the young chicken suffers a loss of the righting reflex. Very small doses (0.02 mcg/kg) induce sleep in young chickens. The depth and the duration of sleep (either behavioural or barbital-or chloral-induced) are potentiated by clonidine in rat, mouse and cat. Given i.v., clonidine produces in rabbits a typical resting EEG. The cat EEG shows synchronization, slower waves and a decrease of faster waves.

In mice the drug has an analgesic action, as these animals do not take up their usual defence and escape reaction. A local anaesthetic action has been observed at very high doses. Clonidine closely resembles the typical local anaesthetic procaine, as shown by electrophysiological studies of intracellular action potentiates and membrane resistance and firing threshold of the crayfish stretch receptor. The local anaesthetic effect of clonidine appears to be much more potent than the effect produced by tetracaine on the rabbit cornea.

Effect on Salivation and Gastric Secretion
Clonidine greatly reduces the conditioned salivation in dogs, but has no effect upon the salivation produced either by pilocarpine or by stimulation of the chorda tympani. The most likely action of the drug is upon central nervous centers controlling salivation, and not by a peripheral effect. Given intravenously, clonidine inhibits the gastric secretion and reduces its acidity in rats, thus giving protection against stress- and reserpine-induced ulcers and gastric haemorrhage, but it is ineffective against histamine- and serotonin-provoked ulcers.

Metabolic effects

Intravenous administration of clonidine increases the pool, life and turnover of body glucose in the rat, and decreases glucose oxidation. There is no change in muscle glycogen, but liver glycogen is lowered. A dose-dependent hyperglycemia has been described in cats receiving clonidine (infusion of 10 mcg/kg. into the vertebral arteries provokes a 30% higher level than control), but this effect is less marked in adrenalectomized animals.

Rabbits show hyperglycemia with very high doses only. Normal and fasting rats also show increased plasma glucose levels after clonidine given by different routes. Clonidine does not

affect the plasma level of free fatty acids, but with very high doses has increased the plasma renin level in rats.

Although single large doses of clonidine impair glucose handling, presumably because of the transient adrenergic effects described above, no effects on glucose metabolism are seen during the long term clinical use of the drug.

TOXICOLOGY

Acute Toxicity

The oral LD_{50} of clonidine in rats was 465 mg/kg, and in mice 206 mg/kg.

The LD_{50} in 24 hours when given intravenously to mice is 17.6 mg/kg; the LD_{50} during a 14-day observation period following a single oral dose is over 30 mg/kg in dogs.

Long Term Toxicity

Subacute (12-13 weeks) and chronic (26-78 weeks) toxicity studies have ruled out any increased morbidity or mortality due to a cumulative effect or possible organ damage. No abnormality has been recorded in blood, urine or internal organs after subacute dosages. In rats, there is a clear dose-related lag in weight gain, and sedation with a brief hyperactive phase immediately following the administration of the drug. Dogs show a dose-related restriction of growth; female dogs in subacute i.v. toxicity studies were anovulatory with high daily doses (0.5 mg/kg.). Glycosuria has been found in rabbits receiving 1 mg/kg daily for 30 days. No significant drug induced pathological or histological change in the circulatory and parenchymatous organs of the rat or in the endocrine organs of mice and rabbits has been observed.

Ophthalmological Toxicity

In several studies, clonidine hydrochloride produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer. Tissue distribution studies in dogs and monkeys revealed that clonidine hydrochloride was concentrated in the choroid of the eye.

In rats, clonidine hydrochloride in combination with amitriptyline produced corneal lesions within 5 days.

Tolerance

Tolerance to clonidine has not been demonstrated in either dogs or in rats, as shown by two exactly measurable parameters (mydriasis and bradycardia).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 132-week (fixed concentration) dietary administration study in rats, clonidine hydrochloride administered at 32 to 46 times the maximum recommended daily human dose was unassociated with evidence of carcinogenic potential. Fertility of male or female rats was unaffected by

clonidine hydrochloride doses as high as 150 mcg/kg or about 3 times the maximum recommended daily human dose (MRDHD). Fertility of female rats did, however, appear to be affected (in another experiment) at dose levels of 500 to 2000 mcg/kg or 10 to 40 times the MRDHD.

Teratogenicity

Reproduction studies performed in rabbits of doses up to approximately 3 times the maximum recommended daily human dose (MRDHD) of clonidine hydrochloride have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the MRDHD were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRDHD) when dams were treated on days 6-15 of gestation. Increased resorptions were observed at much higher levels (40 times the MRDHD) in rats and mice treated on days 1-14 of gestation (lowest dose employed in that study was 500 mcg/kg).

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PART III: CONSUMER INFORMATION
[Pr]MINT-CLONIDINE
Clonidine Hydrochloride Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when MINT-CLONIDINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MINT-CLONIDINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MINT-CLONIDINE tablets are used to provide relief from hot flushes that may occur in women at menopause (change of life).

What it does:
MINT-CLONIDINE tablets helps reduce the frequency, severity and duration of menopausal flushing (due to decreased estrogen levels).

When it should not be used:

Do not take this medicine if:

- You are allergic to clonidine hydrochloride or any other ingredients in MINT-CLONIDINE or have a rare hereditary problem of galactose intolerance or the Lapp lactose deficiency. MINT-CLONIDINE contains lactose.
- You have a severe slow heart rate; MINT-CLONIDINE can lower the heart and pulse rate.

What the medicinal ingredient is:
clonidine hydrochloride.

What the nonmedicinal ingredients are:
The MINT-CLONIDINE (clonidine hydrochloride) tablet core contains the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate, magnesium stearate and pregelatinized maize starch.

The MINT-CLONIDINE tablet coating contains: FD&C Blue #2, hypromellose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

What dosage forms it comes in:
MINT-CLONIDINE is available in tablets. Each tablet contains 0.025 mg of clonidine hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use MINT-CLONIDINE talk to your doctor or pharmacist about any health conditions or problems you may have, including if you:

- have low blood pressure;
- have a slow heart rate, or heart failure, or irregular heart rate, or a recent heart attack;
- have or have had a stroke;
- have poor blood circulation to hands and feet such as Raynaud's syndrome;
- are suffering from constipation;
- have kidney disease;
- have eye problems such as dry eye or wear contact lenses;
- have or have had depression;
- are pregnant or planning to become pregnant;
- are breast-feeding.

MINT-CLONIDINE is not to be used in patients under 18 years of age.

MINT-CLONIDINE may cause sleepiness, dizziness and fainting. Do not drive or operate machinery until you know how the drug affects you.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist all the medicines you are taking including all prescription, non-prescription and natural health products, particularly if you are taking the following medicines:

- drugs that contain clonidine
- drugs that lower blood pressure such as water pills, betablockers, vasodilators, calcium antagonists, ACE-inhibitors
- drugs that slow the heart rate
- drugs for depression and MAO inhibitors
- alpha receptor blockers such as phentolamine
- methylphenidate
- indomethacin and other non-steroidal anti-inflammatory agents
- barbiturates or other sedatives, including alcohol

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions about when and how to take your medicine and always read the label.

Usual dose:
0.05 mg (two 0.025 mg tablets) twice a day. The tablets should be swallowed whole with water.

Do not stop taking MINT-CLONIDINE without talking to your doctor since

stopping MINT-CLONIDINE suddenly may cause a severe withdrawal reaction, which in rare cases can cause death.

Overdose:

If you think you, or a person you are caring for, have taken too much MINT-CLONIDINE, contact a healthcare professional, hospital emergency department, or a regional poison control centre immediately, even if there are no symptoms

Missed Dose:
If you forget to take a dose take one as soon as you remember, then carry on as before.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include: dry mouth, dizziness, tiredness, headache, nausea, vomiting, constipation, feeling weak (malaise), sleepiness, drowsiness and erectile dysfunction (trouble getting or keeping an erection), itchiness, rash, hive, hair loss.

If you experience any of these effects or any other effects not mentioned above and they continue or become troublesome, talk to your doctor or pharmacist.

MINT-CLONIDINE can cause abnormal blood test results. MINT-CLONIDINE may also increase blood sugar, you may need to test your blood sugar more often.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Blood pressure effects:** Fall in blood pressure on standing		√	
	Urinary effects: Urinary difficulty or retention		√	
Uncommon	**Allergic reaction:** Hives, swelling of lips, face or throat with difficulty breathing or speaking (signs of angioedema)			√
	Hypersensitivity reactions: Skin rash, skin eruption or other effect on the skin or eyes		√	
	Muscle or joint effects: Muscle or joint pain and cramps of the lower limbs		√	
	Hallucination: Problem with circulation to the fingers and toes (Raynaud's pheonomenon)		√	
Rare	**Heart effects:** Racing or irregular heart rate, slow heart rate		√	
	Blockage of the large bowel: Colicky pain, constipation, vomiting, liver problems		√	
	Liver disorder: Symptoms such as nausea, vomiting, dark/brown urine		√	
Not Known	Confusion state		√	
	Disability of the eye to change its focus from near	√		

This is not a complete list of side effects. For any unexpected effects while taking MINT-CLONIDINE, contact your doctor or pharmacist.

HOW TO STORE IT

The tablets should not be taken after the expiry date which is printed on the label.

MINT-CLONIDINE tablets should be stored between 15°C - 30°C. Protect from moisture.

Keep this medicine out of the sight and reach of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MINT-CLONIDINE:

- Talk with your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.mintpharmaceuticals.com), or by calling 1-877-398-9696.

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Last revised: January 24, 2023