PRODUCT MONOGRAPH

[Pr]CLONIDINE

(clonidine hydrochloride)

USP Standard

TABLETS

0.025 mg

VASCULAR STABILIZER FOR THE TREATMENT OF MENOPAUSAL FLUSHING

Sanis Health Inc.
333 Champlain Street, Suite 102
Dieppe, New Brunswick
Canada, E1A 1P2

Date of Preparation:
January 6, 2011

Submission Control No: 143935

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 3
ADVERSE REACTIONS 5
DRUG INTERACTIONS 6
DOSAGE AND ADMINISTRATION 7
OVERDOSAGE 7
ACTION AND CLINICAL PHARMACOLOGY 8
STORAGE AND STABILITY 9
DOSAGE FORMS, COMPOSITION AND PACKAGING 9

PART II: SCIENTIFIC INFORMATION 10
PHARMACEUTICAL INFORMATION 10
DETAILED PHARMACOLOGY 11
TOXICOLOGY 16
REFERENCES 18

PART III: CONSUMER INFORMATION 19

[Pr]CLONIDINE
(clonidine hydrochloride)

USP Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 0.025 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE
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
CLONIDINE (clonidine hydrochloride) is contraindicated in patients with known 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.

CLONIDINE is contraindicated in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or atrioventricular block of 2nd or 3rd degree; patients with sinus node function impairment.

WARNINGS AND PRECAUTIONS
General

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

It has been demonstrated that an excessive rise in blood pressure, should it occur on discontinuation of CLONIDINE, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine.

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).

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.

Patients who engage in potentially hazardous activities such as operating machinery or driving should be warned of the possible sedative effect of clonidine hydrochloride. Caution should be exercised in the concomitant administration of sedatives, tranquilizing drugs or alcohol.

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of CLONIDINE 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 CLONIDINE, the physician should reduce the dose gradually over 2-4 days.

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 CLONIDINE.

Carcinogenesis and Mutagenesis
See the TOXICOLOGY section.

Cardiovascular
Because it can lower blood pressure at high doses, CLONIDINE (clonidine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebral vascular disease, or chronic renal failure. 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.

Depending on the dose given, 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.

CLONIDINE should be monitored particularly carefully in patients with heart failure or severe coronary disease.

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 drugrelated 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.

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, CLONIDINE should be used with caution in patients with renal insufficiency. 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.

Special Populations

Pregnant Women: When rats were given clonidine hydrochloride alone in doses as low as one - third the maximum recommended daily human dose, some embryotoxicity was evident (see TOXICOLOGY). There are, however, no adequate and well-controlled studies in pregnant women. Thus, use of clonidine hydrochloride in pregnancy is not recommended.

Nursing Women: The use of CLONIDINE during lactation is not recommended due to a lack of supporting information.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Accumulated clinical and postmarketing data indicate that the most frequently occurring adverse reactions are dryness of mouth, sedation and reduction of blood pressure.

Occasionally, constipation, nausea and vomiting, headache, malaise, impotence, decreased libido, gynaecomastia, orthostatic symptoms, paresthesia of the extremities, Raynauds's phenomenon, pain in the parotid gland, dryness of the nasal mucosa and reduced lacrymal flow

(caution: contact lens wearers) as well as skin reactions with symptoms such as rash, urticaria, pruritus, and alopecia have been observed.

In rare instances, sleep disturbances, nightmares, depression, perceptual disorders, hallucinations, confusion, disturbances of accommodation and transient elevations of blood sugar have been reported.

In very rare cases, pseudo-obstruction of the large bowel has been observed in predisposed patients.

Clonidine may cause or potentiate bradyarrhythmic conditions such as sinus bradycardia or atrioventricular block.

Adverse events reported during treatment with clonidine hydrochloride include, fatigue, muscle or joint pain and cramps, drowsiness and dizziness. In addition, there have been isolated reports of accelerated rate of dental caries due to continual dry mouth, in patients receiving higher doses of clonidine hydrochloride.

DRUG INTERACTIONS

Overview

The doses of clonidine hydrochloride used during clinical trials in menopausal flushing, 0.05 mg b.i.d., did not produce significant changes in blood pressure. Caution should, however, be exercised in patients receiving antihypertensive therapy because of the possibility of an additive effect. The reduction in blood pressure induced by clonidine can be further potentiated by concurrent administration of agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists and ACE inhibitors.

Concomitant use of β-receptor blockers and/or cardiac glycosides can further lower heart rate (bradycardia) or cause dysrhythmia (atrioventricular block) in isolated cases.

It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders.

Orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

Withdrawal of higher doses of clonidine hydrochloride may result in an excess of circulating catecholamines (see WARNINGS). 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, respectively).

If combined treatment with a β-blocker necessitates the interim interruption of antihypertensive therapy or even total discontinuation, the β-blocker must always be discontinued slowly first, reducing the dose gradually to avoid sympathetic hyperactivity. Clonidine hydrochloride must then be reduced gradually over several days if previously given in high dosages.

If clonidine hydrochloride and tricyclic antidepressants are administered as concurrent therapy, the effect of clonidine hydrochloride may be reduced, thus necessitating an increase in the dosage of CLONIDINE. Amitriptyline in combination with clonidine hydrochloride enhances the manifestation of corneal lesions in rats (see TOXICOLOGY).

Clonidine hydrochloride may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives.

Substances with alpha$_2$-receptor blocking properties such as phenolamine or tolazoline may abolish the alpha$_2$-receptor mediated effects of clonidine in a dose-dependent manner. Therefore, depending upon the dose administered, tolazoline is suitable as an antidote.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose for the treatment of menopausal flushing is 0.05 mg of 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.

Missed Dose

If a dose of 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, diminished or absent reflexes, vomiting and hypoventilation. With large overdoses, reversible cardiac conduction defects or arrhythmias, coma, 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.

Clonidine overdosage usually responds to symptomatic treatment, volume expansion for hypotension and careful cardiovascular monitoring. Gastric lavage, followed by administration of activated charcoal if a large dose has been taken, can be initiated within two hours of ingestion

if the airway can be protected. Routine hemodialysis is of limited benefit since a maximum of 5% of circulating clonidine is removed.

Intravenous naloxone has been used as antidotes to clonidine poisoning, with inconsistent results. If other efforts fail, these agents may provide some benefit in reversing the effects of clonidine.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 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.

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.

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. The plasma level of clonidine peaks in approximately 3 to 5 hours and the plasma half-life from 12-16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

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_{o} 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

In man, a significant plasma level (0.20 µg% of clonidine) can be detected one hour after oral administration of a single dose of 390 µg. Since clonidine is approximately 50% bound, this reflects an actual free plasma level.

Sixty-five percent (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.

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.

STORAGE AND STABILITY

CLONIDINE tablets should be stored at controlled room temperature (15-30°C). Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

0.025 mg tablet: Blue, round, biconvex, film-coated tablets, engraved **N** on one side and plain on the other side.

Composition

The CLONIDINE (clonidine hydrochloride) tablet core contains clonidine HCI and the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch.

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

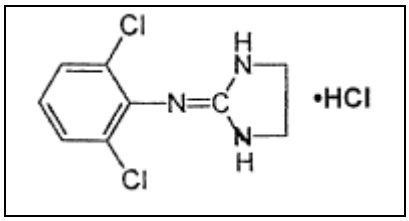
Packaging

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	clonidine hydrochloride
Proprietary Name	CLONIDINE
Chemical Name	2-[(2,6-Dichlorophenyl)imino]imidazolidine monohydrochloride
Structural Formula	
Molecular Formula	$C_9H_9N_3Cl_2$•HCl
Molecular Weight	266.56
Description	Clonidine hydrochloride occurs as white crystalline powder. It is soluble in water methanol and ethanol; slightly soluble in chloroform. The pH of a 5% aqueous solution lies between 4 and 5.

CLINICAL STUDIES

COMPARATIVE BIOAVAILABILITY STUDY

An evaluation of the comparative bioavailability between Clonidine 0.025 mg Tablets (Sanis Health Inc.) and Dixarit® 0.025 mg Tablets (Boehringer Ingelheim Ltd., Canada) after a single-dose in 24 healthy male and female volunteers under fasting conditions. A summary of the results is presented below.

Clonidine (2 x 0.025 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg.h/ml)	2768.38 2848.83 (24)	2691.99 2779.65 (25)	102.84	98.60 - 107.26
AUC_I (pg.h/ml)	2944.42 3052.03 (27)	2863.63 2968.03 (27)	102.82	98.53 - 107.30
C_{max} (pg/ml)	186.14 188.96 (18)	185.64 190.21 (24)	100.27	96.47 - 104.22
T_{max} § (h)	2.12 (37)	2.03 (37)		
$T_{½}$ § (h)	11.39 (27)	11.18 (21)		

*Clonidine 0.025 mg Tablets (Sanis Health Inc., Canada)
† Dixarit® 0.025 mg Tablets (Boehringer Ingelheim (Canada) Ltd., Canada)
§ 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 µg% of clonidine) can be detected one hour after oral administration of a single dose of 390 µg. 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 μg/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 µg/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 µg/kg/day for 4 weeks or 20 µg/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 µg/kg of clonidine either before or after ganglion blockade as well as after seven days of intramuscular administration of 20 µg/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 μg/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 μg/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 µg/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 µg/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 µg/kg).

REFERENCES

1. Barr W. Problems related to post-menopausal women. S Afr Med J 1 975; 49: 437-39.

2. Bolli P, Simpson OF Clonidine in menopausal flushing: a double-blind trial. NZ Med J 1975; 82(548):196-7.

3. Broadhurst ER. Oestrogens for menopausal flushing. Reply by A Klopper. Br Med J 1976; 2(6037):697.

4. Buckingham L, et al. Menopausal flushing - an alternative to oestrogen therapy Med J Aust 1976; 63(2):546.

5. Clayden JR, et al. Menopausal flushing: double-blind trial of a non-hormonal medication. Br Med J 1974; 1:409.

6. Clayden JR. Effect of clonidine on menopausal flushing. Lancet 1972; 2: 1361.

7. Clayden JR, Bell JW. Control of menopausal flushes. Br,Med J 1973;4:44.

8. Clayden JR, Bell JW. Control of menopausal flushes. Br Med J 1974; 1:113,

9. Clayden JR. Dixarit and the menopause - a preliminary report. Proc Symposium, Churchill College, Cambridge, 1972: July; 92-9.

10. Dollery CT, et al. Clinical pharmacology and pharmacokinetics of clonidine. Clin Pharmacol Ther 1976; 19: 11-17.

11. Edington RF, et al. Clonidine (Dixarit) for menopausal flushing. Can Med Assoc J 1980; 123:23-6,

12. Gaskell P, Melnyk J. The effect of clonidine on vascular reactivity to angiotensin, noradrenaline and vasopressin in conscious rats. Can J Physiol Pharm 1978; 56:23-9,

13. Kowal L. Menopausal flushing - an alternative to oestrogen therapy. Med J Aust 1976; 63(2):733.

14. Ylilorkala 0. Clonidien in the treatment of menopausal symptoms. Ann Chir Gynaecol Fenn 1975; 64(4):242-5.

15. Zaimis E. Possible pharmacological approach to migraine. Lancet 1969;2:298.

16. Lowenthal DT. Pharmacokinetics of Clonidine. J Cardiovasc Pharmacol 1980;2:S29-S37.

17. Dixarit® Product Monograph, Boehringer Ingelheim (Canada) Limited, Control Number: 109237, Date of Revision: January 20, 2007.

18. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Clonidine Hydrochloride 0.025 mg Tablets Under Fasting Conditions.

PART III: CONSUMER INFORMATION
Pr CLONIDINE
(clonidine hydrochloride) Tablet

This leaflet is part III of a three-part "Product Monograph" published when 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 CLONIDINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

What it does:
CLONIDINE Tablets belong to a group of medicines called vasodilators which cause widening of the blood vessels and therefore an increase in blood flow. This results in a reduction in the frequency, severity and duration of hot flushes attacks associated with menopause. CLONIDINE will not correct or relieve other menopausal changes that are due to hormonal deficiencies. The response to CLONIDINE is gradual and once you stop taking it, there is a gradual return of the symptoms.

When it should not be used:
Tell your doctor or pharmacist if you say yes to any of the following as you should not take this medicine:

- You are hypersensitive or "allergic" to the active ingredient clonidine hydrochloride or any other ingredient in this product
- You have a slow heart rate due to heart problems

What the medicinal ingredient is:
CLONIDINE tablets contain the active ingredient called clonidine hydrochloride.

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

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

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

WARNINGS AND PRECAUTIONS

BEFORE you use CLONIDINE talk to your doctor or pharmacist if you say yes to any of the following:

- You are pregnant, planning to become pregnant or if you are breast feeding
- You suffer from heart or kidney problems
- You suffer from Raynaud's disease or other circulation problems
- You have any problems with circulation of blood to your brain
- You are suffering from constipation
- You are suffering from or have, in the past, suffered from depression
- You have been told by your doctor that you have an intolerance to some sugars as CLONIDINE Tablets contain lactose.
- You drink alcohol

If in doubt, ask your doctor or pharmacist.

CLONIDINE is not to be used in children under 18 years of age.

CLONIDINE may cause drowsiness which can be made worse by taking alcohol, sedatives or tranquilizers. If affected, do not drive or operate machinery and avoid taking alcohol, sedatives or tranquilizers.

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:

- any other medicine containing clonidine
- antihypertensives (medicines that lower blood pressure)
- vasodilators (e.g. sodium nitroprusside)
- diuretics (commonly called water tablets e.g. furosemide) beta-blockers (e.g. atenolol)
- alpha-blockers (e.g. phenolamine and tolazoline)
- cardiac glycosides (e.g. digoxin)
- tricyclic antidepressants (e.g. imipramine)
- other antidepressants (e.g. mirtazipine)
- neuroleptics (e.g. phenothiazines)
- tranquillisers (e.g. chlorpromazine)
- hypnotics (medicines to help you sleep or for anxiety)

PROPER USE OF THIS MEDICATION

Usual dose:

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

The usual recommended dose is 0.05 mg (two 0.025 mg tablets) twice a day. The tablets should be swallowed whole with water.

Do not change your dose or stop taking CLONIDINE without first talking to your doctor.

Overdose:
In case of accidental overdose, consult a physician immediately or contact your regional Poison Control Centre. Always take the labelled medicine container with you whether or not there are any CLONIDINE Tablets left.

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

Like all medicines, CLONIDINE can have side-effects. Most side effects are mild and decrease with continued treatment. If you experience any of these side effects and they persist or become troublesome contact your doctor.

The most frequently occurring side effects are:
- dryness of mouth
- sedation
- lowering of blood pressure

Less frequently occurring side effects are:
- constipation
- nausea (feeling sick)
- vomiting,
- headache
- malaise (a vague feeling of discomfort and fatigue)
- impotence
- decreased libido (sex drive)
- gynaecomastia (enlargement of male breast tissue)
- orthostatic symptoms (fall in blood pressure on standing)
- paresthesia of the extremities (altered sensation at the finger tips, toes, etc)
- Raynauds's phenomenon (a problem with circulation to the fingers and toes
- pain in the parotid gland (gland below the ear)
- dryness of the lining of the nose
- reduction in the production of tears in the eyes (this may be a problem for people who wear contact lens)
- skin reactions such as rash, urticaria (nettle rash), itching
- hair loss

Rarely occurring side effects are:
- sleep disturbances
- nightmares
- depression
- perceptual disorders
- hallucinations
- confusion
- disturbances of accommodation
- transient rise of blood sugar

Very rarely occurring side effects are:
Pseudo-obstruction of the large bowel in predisposed patients (symptoms include: colicky pain, constipation and vomiting)

CLONIDINE may increase the possibility of irregular or slow beating of the heart.

Adverse events reported during treatment with CLONIDINE include fatigue, muscle or joint pain and cramps, drowsiness and dizziness. In addition, there have been rare cases of increased dental cavities due to continual dry mouth, in patients receiving higher doses of clonidine hydrochloride.

If you experience any other side-effects not mentioned above, consult your doctor or pharmacist.

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 call your doctor or pharmacist
		Only if severe	In all cases	
Common	Drop in blood pressure		✓	
Uncommon	Irregular or slow beating of the heart		✓	

This is not a complete list of side effects. For any unexpected effects while taking 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.

CLONIDINE Tablets should be stored at room temperature (15- 30°C). Protect from moisture.

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

REPORTING SUSPECTED SIDE EFFECTS

IMPORTANT: PLEASE READ

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full Prescribing Information, prepared for health professionals can be found at: 1-866-236-4076

This leaflet was prepared by:
Sanis Health Inc.
333 Champlain Street, Suite 102
Dieppe, New Brunswick
Canada, E1A 1P2

Last revised: January 6, 2011