PRODUCT MONOGRAPH

PrTEVA-CLONIDINE

(Clonidine Hydrochloride)

0.1 mg and 0.2 mg Tablets

USP

Antihypertensive

Teva Canada Limited
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Toronto, Ontario
M1B 2K9

Date of Revision:
April 25, 2014

Submission Control No: 171843

Table of Contents

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(Clonidine hydrochloride Tablets)
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Nonmedicinal Ingredients
Oral	Tablets 0.1 mg, 0.2 mg	0.1 mg tablets contain, in addition to clonidine hydrochloride, the following non-medicinal ingredients: colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch. 0.2 mg tablets contain, in addition to clonidine hydrochloride, the following non-medicinal ingredients: colloidal silicon dioxide, dibasic calcium phosphate, FD&C Yellow #6 lake, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch. *See Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TEVA-CLONIDINE (clonidine hydrochloride) is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics. Clonidine should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

TEVA-CLONIDINE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Pediatrics (< 18 years of age):

Safety and effectiveness in children have not been established.

CONTRAINDICATIONS

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

Patients who are hypersensitive to this drug or to any ingredients in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

TEVA-CLONIDINE is also contraindicated in patients with the rare hereditary condition of galactose intolerance e.g. galactosaemia. TEVA-CLONIDINE tablets contain approximately 534 mg of lactose monohydrate per maximum recommended daily dose (0.6 mg) and thus should not be used by patients with this condition.

WARNINGS AND PRECAUTIONS

General

Patients should be instructed not to discontinue therapy without consulting their physician. A pronounced withdrawal reaction with symptoms suggesting sympathetic over-activity may develop within 12 to 48 hours when clonidine is discontinued. High serum levels of catecholamines have been found during such episodes (see DRUG INTERACTIONS). When discontinuing TEVA-CLONIDINE (clonidine hydrochloride) therapy, the physician should reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, restlessness, palpitations, tremor, nausea and headache. Rare instances of hypertensive encephalopathy and death have been recorded after abrupt cessation of clonidine hydrochloride therapy. A withdrawal reaction is most likely to occur in patients who have been receiving large doses (greater than 1.2 mg/day) or in those who are continuing to receive a concomitant beta-blocker. If therapy is to be discontinued in patients receiving clonidine and a β adrenergic blocking agent concomitantly, the β blocker should be first phased out gradually before clonidine therapy is discontinued.

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

Clonidine is not indicated in pheochromocytoma. However, in contrast to guanethidine and reserpine the drug has no crisis-inducing properties, in this condition.

Clonidine does not affect the urinary vanilmandelic acid (VMA) and catecholamine excretion significantly in patients with pheochromocytoma, so that no false positive or false negative results will occur during the administration of the drug.

Pediatrics (< 18 years of age):

Safety and effectiveness in children have not been established and therefore cannot be recommended for use in this population.

Carcinogenesis and Mutagenesis

See PART II: TOXICOLOGY section.

Cardiovascular

Because it lowers blood pressure, TEVA-CLONIDINE (clonidine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

TEVA-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, and in patients with heart failure or severe coronary heart disease.

The dosage of clonidine hydrochloride should be increased gradually to minimize the sedative effect of the drug. This is of particular importance in those patients who operate automobiles and potentially dangerous machinery (see WARNINGS AND PRECAUTIONS: Effects on ability to drive and use machines).

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

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

A few instances of a condition resembling Raynaud's phenomenon have been reported. Caution should therefore be observed if patients with Raynaud's disease or thromboangiitis obliterans are to be treated with clonidine.

Dependence/Tolerance

Tolerance may develop in some patients, necessitating a re-evaluation of therapy. This usually consists of an increase in dosage or concomitant administration of a diuretic to enhance the hypotensive response to the drug.

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 PART II: TOXICOLOGY). In view of this retinal degeneration, eye examinations were performed in 908 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. It is

recommended that as an integral part of their overall long-term care, patients treated with TEVA-CLONIDINE should receive periodic eye examinations.

Patients who wear contact lenses should be warned that treatment with TEVA-CLONIDINE may cause decreased lacrimation (see ADVERSE REACTIONS: Eye disorder).

Peri-Operative Considerations

Administration of TEVA-CLONIDINE should be continued to within four hours of surgery and resumed as soon as possible thereafter. The blood pressure should be carefully monitored and appropriate measures instituted to control it as necessary.

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 the urine. Renal insufficiency requires particularly careful adjustment of dosage.

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: Reproduction studies performed in rabbits at doses up to approximately 3 times the maximum recommended daily human dose (MRDHD) of clonidine hydrochloride has revealed no evidence of teratogenic or embryotoxic potential in rabbits. When rats were given clonidine hydrochloride alone in doses as low as one-third the MRDHD, some embryotoxicity was evident (see PART II: TOXICOLOGY).

There are, however, limited amount of data from the use of clonidine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Careful monitoring of the mother and child is recommended. Clonidine hydrochloride passes the placental barrier and may lower the heart rate of the fetus. A postpartum transient rise in blood pressure in the newborn cannot be excluded. There is no adequate experience regarding the long-term effect of prenatal exposure.

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

Pediatrics (< 18 years of age): Safety and effectiveness in children have not been established and therefore cannot be recommended for use in this population.

Fertility

No clinical studies on the effect on human fertility have been conducted with clonidine. Non-clinical studies with clonidine indicate no direct or indirect harmful effects with respect to the fertility index (see PART II: TOXICOLOGY).

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, and accommodation disorder during treatment with TEVA-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 generally tend to diminish with continuation of therapy. The most common are sedation (about 50%), dry mouth (about 44%), orthostatic hypotension (about 19%) and dizziness (about 15%).

The most serious reactions have been reported upon abrupt discontinuation of the drug (see WARNINGS AND PRECAUTIONS - Withdrawal). The potentially serious adverse drug reactions are the following:
Psychiatric disorders: confusional state, depression, hallucination
Nervous system disorders: dizziness, sedation
Cardiac disorders: atrioventricular block, bradyarrhythmia, sinus bradycardia.
Vascular disorders: orthostatic hypotension, Raynaud's phenomenon
Gastrointestinal disorders: colonic pseudo-obstruction
The above-mentioned serious adverse drug reactions could result in clinical intervention.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

from clinical trials is *useful for identifying drug-related adverse events and for approximating rates.*

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.

Table 1: Adverse events occurring in ≥ 1 % of the clonidine hydrochloride patients in placebo-controlled clinical trials

System Organ Class (SOC)	**Preferred MedDRA Term**	**Clonidine Hydrochloride n = 640 %**
Psychiatric disorders	Depression	1
	Sleep disorder	5
Nervous system disorder	Dizziness	15
	Headache	1
	Sedation	50
Vascular disorders	Orthostatic hypotension	19.3
Gastrointestinal disorders	Constipation	4
	Dry mouth	44
	Nausea	1.25
	Salivary gland pain	2
	Vomiting	1.25
Reproductive system and breast disorders	Erectile dysfunction	4
General disorders	Fatigue	1

Most adverse reactions associated with the use of clonidine hydrochloride are mild and generally tend to diminish with continuation of therapy.

Less Common Clinical Trial Adverse Drug Reactions

In addition, the following potentially important events occurred in less than 1% of patients receiving clonidine hydrochloride:

Cardiac disorders:
atrioventricular block, bradyarrhythmia, sinus bradycardia

Endocrine disorders:
gynaecomastia

Eye disorder:
accommodation disorder, lacrimation decreased

Gastrointestinal disorders:
colonic pseudo-obstruction, accelerated rate of dental caries

General disorders and administration site conditions:
malaise

Nervous system disorders:
paraesthesia

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

Respiratory, thoracic and mediastinal disorders:
nasal dryness

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

Vascular disorders:
Raynaud's phenomenon

Abnormal Hematologic and Clinical Chemistry Findings

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.	
β -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	

Proper name	References	Effect	Clinical comment
		administration will cause or potentiate peripheral vascular disorders.	
Tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties	Briant RH et al, 1973 (48) Hui KK et al, 1983 (49) Fruncillo RJ et al, 1985 (50) (See REFERENCES)	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 PART II: TOXICOLOGY).	If clonidine hydrochloride and tricyclic antidepressants are administered as concurrent therapy, an increase in the dosage of clonidine hydrochloride 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.	
Appetite suppressants (with the exception of fenfluramine)		Concurrent use with clonidine hydrochloride may decrease the hypotensive effects of clonidine hydrochloride. Concurrent use of fenfluramine and clonidine hydrochloride may increase the hypotensive effects of clonidine hydrochloride.	
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 these amines (monoamine oxidase (MAO) inhibitors, tricyclic		Withdrawal of clonidine hydrochloride may result in an excess of circulating catecholamines (see WARNINGS AND	Caution should be exercised in concomitant use of these drugs.

Proper name	References	Effect	Clinical comment
antidepressants and beta blocking agents, respectively).		PRECAUTIONS).	
Methylphenidate	Popper CW, 1995 (52) (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

Dosing Considerations

Treatment of hypertension requires regular medical supervision.

The dose of TEVA-CLONIDINE (clonidine hydrochloride) must be adjusted according to the patient's individual blood pressure response.

Recommended Dose and Dosage Adjustment

Initial Dose: 0.1 mg tablet twice daily (morning and bedtime).

Maintenance Dose: After a period of 2-4 weeks, further increments of 0.1 mg per day may be necessary until the desired response is achieved. In those instances where it is not possible to have equal amounts of drug at each of the dosing intervals, taking the larger portion of the total daily dose at bedtime may minimize transient adjustment effect of dry mouth and drowsiness.

The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day given in divided doses. Usually doses above 0.6 mg per day do not result in a further marked reduction in blood pressure.

Discontinuation of Treatment: If TEVA-CLONIDINE (clonidine hydrochloride) is to be discontinued, reduce dosage gradually (see WARNINGS AND PRECAUTIONS).

Missed Dose

If a dose of TEVA-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.

Use in Elderly
Elderly patients may benefit from a lower initial dose.

Use in Impaired Renal Function
Doses must be adjusted according to the degree of impairment and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine during dialysis.

Use in Impaired Hepatic Function
Dosage instructions for patients with impaired hepatic function have not been established.

Use in Children
The safety and efficacy of clonidine have not been established in children.

OVERDOSAGE

The signs and symptoms of clonidine hydrochloride overdosage include generalised 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 induction defects or arrhythmias, coma, respiratory depression including apnoea, 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, apnoea, 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 ingestions 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, this agent may provide some benefit in reversing the effects of clonidine.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Clonidine hydrochloride is α andrenergic agonist which also has some α adrenergic antagonist effects. The antihypertensive effect of clonidine hydrochloride is thought to be due to central α_2 adrenergic stimulation, which results in a decreased sympathetic outflow to the heart, kidneys, and peripheral vasculature and thus decreased peripheral vascular resistance, decreased systolic and diastolic blood pressure and decreased heart rate. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact and therefore orthostatic symptoms are mild and infrequent. Acute studies with clonidine hydrochloride in humans have demonstrated a moderate reduction (15% to 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 of peripheral resistance. During long-term therapy, cardiac output tends to return to control 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.

Prolonged treatment with clonidine hydrochloride in animals causes a decrease in the responsiveness of the vascular smooth muscle to catecholamines and angiotensin. The change in vascular response may be of importance in explaining the chronic hypotensive effect in man.

Acute administration of clonidine stimulates the release of growth hormone in children and adults, but the drug does not produce sustained elevation of growth hormone during chronic administration.

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 man, the blood pressure reduction due to 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.

Pharmacokinetics

Absorption: The plasma level of clonidine hydrochloride peaks in approximately 1 to 3 hours. In humans, a significant plasma level (0.20 µg% of clonidine) can be detected one hour after oral administration of a single dose of 390 µg.

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. However, there is insufficient information on the effect in 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.

Special Populations and Conditions

Renal Insufficiency: Doses must be adjusted according to the degree of impairment and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine during dialysis.

STORAGE AND STABILITY

Store between 15°C - 30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

TEVA-CLONIDINE (clonidine hydrochloride) is available as:

0.1 mg tablets: white round flat-faced bevel-edged compressed tablets, engraved with no | ov on one side and 0.1 on the reverse.

0.2 mg tablets: orange coloured round flat-faced bevel-edged compressed tablets, engraved with no | ov on one side and 0.2 on the reverse.

Composition

The TEVA-CLONIDINE 0.1 mg tablets contain, in addition to clonidine hydrochloride, the following non-medicinal ingredients: colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch.

The TEVA-CLONIDINE 0.2 mg tablets contain, in addition to clonidine hydrochloride, the following non-medicinal ingredients: colloidal silicon dioxide, dibasic calcium phosphate, FD&C Yellow #6 lake, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch.

Packaging

TEVA-CLONIDINE 0.1mg and 0.2 mg tablets are supplied in bottles of 100 and 500 and boxes of 100 as unit dose strips.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

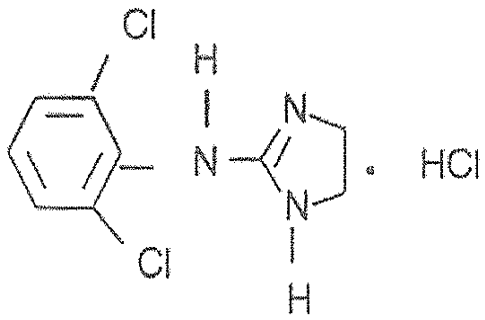
Drug Substance

Proper name: clonidine hydrochloride

Chemical name:
2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride

Molecular formula and molecular mass: $C_9H_9N_3C1_2 \cdot HCl$, 266.56 g/mol

Structural formula:



Physicochemical properties: A white, odorless, bitter, crystalline powder. It is soluble in water and alcohol, practically insoluble in chloroform and ether. The pH of a 5% aqueous solution lies between 3.5 and 5.5.

CLINICAL STUDIES

COMPARATIVE BIOAVAILABILITY STUDY

A single dose, crossover comparative bioavailability study of 2 x 0.2 mg TEVA-Clonidine tablets and 2 x 0.2 mg Catapres® tablets in 18 adult healthy male volunteers was conducted under fasting conditions. The results of the study can be summarized as follows:

Clonidine (2 x 0.2 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 95%
AUC_T (ng•h/mL)	17.5 17.8 (20.1)	17.6 18.2(25.5)	94.7	86.1 – 103.4
AUC_I (ng•h/mL)	18.9 19.4 (19.8)	19.5 19.9 (24.4)	94.2	86.5 – 101.7
C_{max} (ng/mL)	1.2 1.2 (13.7)	1.2 1.2 (18.3)	97.3	89.6 – 104.8
T_{max}§ (h)	2.5 (1.0)	2.9 (1.5)		
$T_{½}$§ (h)	10.3 (3.1)	11.8 (3.7)		

*Teva-Clonidine 0.2 mg Tablets manufactured by Teva Canada Limited, Canada.
† Catapres® 0.2 mg Tablets, Boehringer Ingelheim (Canada) Ltd, were purchased in 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 30-40% 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 5 to 25.5 hours. Elimination decreases after 24 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 hydrochloride after oral administration is found in the kidneys and the gastrointestinal tract, but only very small amounts can be detected in these organs 48 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 24-28 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 faeces. In man, 65% of the orally administered drug is excreted in the urine, and an estimated 22% in the faeces. 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 pg/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 pretreatment 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 mg/kg i.v. in experimental animals, but total denervation of the heart abolishes any bradycardic response to 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 cardio-accelerator 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 µ*g/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 epinehrine, 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 µ*g/kg* of clonidine, either before or after ganglion blockade as well as after seven days of intramuscular administration of 20 µ*g/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 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 therapy. 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 potentials 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 pg/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 not shown 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 have been observed.

Ophthalmologic 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 one 32-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 at 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).

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PART III: CONSUMER INFORMATION

Pr**TEVA-CLONIDINE**(Clonidine Hydrochloride) Tablet

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

ABOUT THIS MEDICATION

What the medication is used for:

TEVA-CLONIDINE tablets help reduce high blood pressure in patients that did not respond or who experienced unacceptable adverse events when using other medicines for high blood pressure.

What it does:

TEVA-CLONIDINE tablets belong to a group of medicines called antihypertensives which are used to reduce high blood pressure.

The clonidine hydrochloride ingredient of TEVA-CLONIDINE is a vasodilator which causes widening of the blood vessels and therefore an increase in blood flow. When there is less resistance to blood flow, blood pressure is lowered.

When it should not be used:

Do not take TEVA-CLONIDINE if you:

- Are hypersensitive or "allergic" to the active ingredient clonidine hydrochloride or any other ingredient in this product or component of the container, (see **'What the non-medicinal ingredients are:'** section)
- Have a slow heart rate due to heart problems
- Have galactosaemia (a rare genetic condition causing galactose intolerance)

What the medicinal ingredient is:

clonidine hydrochloride.

What the non-medicinal ingredients are:

The TEVA-CLONIDINE 0.1 mg tablets contain: colloidal silicon dioxide, dibasic calcium phosphate, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch.

The TEVA-CLONIDINE 0.2 mg tablets contain: colloidal silicon dioxide, dibasic calcium phosphate, FD&C yellow #6 lake, lactose monohydrate (spray dried), magnesium stearate and pregelatinized starch.

What dosage forms it comes in:

Tablet; 0.1 mg (white), 0.2 mg (orange)

WARNINGS AND PRECAUTIONS

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

- have Raynaud's disease or other circulation problems
- have any problems with circulation of blood to your brain
- have heart or kidney problems
- have a slow heart rate
- are suffering from constipation
- have symptoms of nerve disorders (such as altered sensation of the extremities or low blood pressure upon standing)
- have been told by your doctor that you have galactose intolerance
- are suffering from or have, in the past, suffered from depression
- are pregnant, planning to become pregnant or if you are breast feeding
- have pheochromocytoma (tumour of the adrenal gland)

TEVA-CLONIDINE is not recommended for use in children and adolescents (under the age of 18 years).

Other warnings you should know about:

TEVA-CLONIDINE tablets may cause drowsiness. If affected do not drive or operate machinery and avoid alcohol, sedatives or tranquilizers.

INTERACTIONS WITH THIS MEDICATION

Before taking TEVA-CLONIDINE, tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines, and:

- any other medicine containing clonidine
- diuretic tablets (commonly called water tablets e.g. furosemide)
- other medicines to treat high blood pressure (e.g. beta blockers)
- alpha blockers (e.g. phentolamine)
- tricyclic antidepressants (e.g. imipramine)
- major tranquilizers (e.g. chlorpromazine)
- non-steroidal anti-inflammatory agents (e.g. ibuprofen)
- vasodilators (e.g. sodium nitroprusside)
- calcium antagonists (e.g. verapamil, diltiazem hydrochloride)
- ACE inhibitors (e.g. captopril, lisinopril)
- cardiac glycosides (e.g. digoxin)
- tablets which cause drowsiness
- tablets to decrease appetite

- neuroleptics (e.g. phenothiazines)

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions about when and how to take your medicine and always read the label. Do not change your dose or stop taking TEVA-CLONIDINE without first talking to your doctor.

Usual dose:
Initial dose: The usual starting dose is 0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose.

Maintenance dose: After a period of 2 to 4 weeks, a higher dose may be needed until the desired response is achieved. In those instances where it is not possible to take the same dose of the drug in the morning and at bedtime, taking the larger dose at bedtime may help reduce the dry mouth and drowsiness side effects.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Always take the labelled medicine container with you whether or not there are any TEVA-CLONIDINE tablets left.

Missed Dose:
If you forget to take your medicine, take your dose when you remember and then your next dose at the usual time. If you forget a dose completely, do not take two doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including TEVA-CLONIDINE, may cause side effects. Most adverse events are mild and tend to diminish with continuation of therapy.

Side effects may include: dry mouth, dizziness, fatigue, headache, nausea, vomiting, constipation, malaise, sleep disorder, sedation and erectile dysfunction.

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

With the exception of allergic reaction, you should not stop taking TEVA-CLONIDINE without first consulting with your doctor as this may cause a severe withdrawal reaction which in rare cases can cause death.

TEVA-CLONIDINE can cause abnormal blood test results. They may indicate excess sugar in blood. Your doctor will decide when to perform blood tests and will interpret the results.

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 to distant objects	√		

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

HOW TO STORE IT

TEVA-CLONIDINE Tablets: Store between 15°C - 30°C. Protect from moisture.

Do not take this medicine after the expiry date which is printed on the packaging.

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals can be found by contacting
Teva Canada Limited
at: 1-800-268-4127 ext. 1255005 (**English**)
or 1-877-777-9117 (**French**)
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Last revised: April 25, 2014