PRODUCT MONOGRAPH

[Pr] MYLAN-CANDESARTAN HCTZ

Candesartan Cilexetil/Hydrochlorothiazide Tablets

16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg

Angiotensin II AT_1 Receptor Blocker + Diuretic

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet: 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg	Carmellose calcium, glyceryl monostearate, hydroxypropylcellulose, iron oxide red (16 mg/12.5 mg and 32 mg/25 mg strengths only), iron oxide yellow, lactose monohydrate, magnesium stearate and maize starch

INDICATIONS AND CLINICAL USE

Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

Mylan-Candesartan HCTZ is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

The dosage of Mylan-Candesartan HCTZ must be individualized. The dose of Mylan-Candesartan HCTZ should be determined by titration of the individual components.

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended.

Pediatrics (< 18 years of age): The safety and efficacy of Mylan-Candesartan HCTZ have not been established in children.

CONTRAINDICATIONS

Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) is contraindicated in:

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

- Patients with anuria and patients who are hypersensitive to other sulfonamide-derived drugs, because of the hydrochlorothiazide component (see WARNINGS AND PRECAUTIONS, Immune and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

- Pregnant women (see WARNINGS AND PRECAUTIONS, **Special Populations**, **Pregnant Women**).

- Nursing women (see WARNINGS AND PRECAUTIONS, **Special Populations**, **Nursing Women**).

- Children aged < 1 year.

- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2) (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs).

- Patients with severe hepatic impairment and/or cholestasis.

- Patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2 BSA).

- Patients with gout.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, Mylan-Candesartan HCTZ should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as the candesartan cilexetil component of Mylan-Candesartan HCTZ, or of angiotensin converting enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2). Therefore, the use of Mylan-Candesartan HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including the candesartan cilexetil component of Mylan-Candesartan HCTZ, with other agents blocking the RAS, such as ACEIs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, decreased renal function (including acute renal failure), and hyperkalemia.

Avoid the concomitant use of ACE inhibitors and ARBs in patients with diabetic nephropathy.

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of candesartan cilexetil. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, or undergoing surgery with anaesthesia. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or

cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Endocrine and Metabolism

Metabolism

Patients receiving thiazides, including hydrochlorothiazide (HCTZ), should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia).

Periodic determinations of serum electrolytes, to detect possible electrolyte disturbance, should be performed at appropriate intervals. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Thiazides may decrease serum PBI (protein bound iodine) levels without signs of thyroid disturbance.

Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Treatment with a thiazide diuretic may impair glucose tolerance. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. However, at the doses contained in candesartan cilexetil/hydrochlorothiazide, minimal effects were observed.

General

Driving and Operating Machinery

The effect of candesartan cilexetil/hydrochlorothiazide on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties candesartan cilexetil/hydrochlorothiazide is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid or electrolyte balance may precipitate hepatic coma.

Dose titration is recommended in patients with mild to moderate chronic liver disease (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Mylan-Candesartan HCTZ is contraindicated in patients with severe hepatic failure and/or cholestasis (see CONTRAINDICATIONS).

No studies were carried out with candesartan cilexetil/hydrochlorothiazide fixed combination in patients with impaired hepatic function.

Immune

Hypersensitivity Reactions

Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Ophthalmologic

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue Mylan-Candesartan HCTZ as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Peri-Operative Considerations

Thiazides may increase the responsiveness to tubocurarine.

Renal

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

The use of ARBs, including the candesartan cilexetil component of Mylan-Candesartan HCTZ, or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Use of candesartan cilexetil should include appropriate assessment of renal function. Thiazides should be used with caution.

In patients with mild to moderate renal impairment (ie, creatinine clearance between 30-80 mL/min/1.73m^2 BSA), a dose titration is recommended (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Because of the hydrochlorothiazide component, Mylan-Candesartan HCTZ is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2 BSA) (see CONTRAINDICATIONS).

Renal Transplantation

There is limited experience regarding the administration of candesartan in patients with renal transplant.

Azotemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Special Populations

Pregnant Women:

Mylan-Candesartan HCTZ is contraindicated during pregnancy (see CONTRAINDICATIONS). Drugs that act directly on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Mylan-Candesartan HCTZ should be discontinued as soon as possible.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACEIs during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARBs, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ARBs should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during pregnancy may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Animal Data: Oral doses ≥ 10 mg candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or

external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses ≤1000 mg candesartan cilexetil/kg/day were administered to pregnant mice.

Nursing Women:
It is not known whether candesartan is excreted in human milk, but significant levels have been found in the milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk, and because of their potential for adversely affecting the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age):
The safety and efficacy of Mylan-Candesartan HCTZ have not been established in children.

Mylan-Candesartan HCTZ is contraindicated in children aged < 1 year (see CONTRAINDICATIONS).

In utero exposure: Infants with a history of *in utero* exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Candesartan cilexetil is not removed from plasma by dialysis.

Geriatrics (> 65 years of age):

No overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Candesartan cilexetil/hydrochlorothiazide has been evaluated for safety in over 2500 patients treated for hypertension, including more than 700 treated for six months or more, and 500 for about one year or more. In placebo controlled double blind studies to support candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg, candesartan cilexetil/hydrochlorothiazide combination was administered to 1025 hypertensive patients. Approximately 600 patients received candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg. The overall exposure amounts to 977 patient-years. Safety of the higher strength combinations of candesartan cilexetil/hydrochlorothiazide, 32 mg / 12.5 mg and 32 mg / 25 mg, has also been evaluated. In controlled clinical studies 718 patients were treated with candesartan/hydrochlorothiazide 32 mg / 12.5 mg and 1155 patients were treated with 32 mg / 25 mg; the total exposure in patient years in these studies was 107.8 and 175.3 years, respectively.

In general, adverse events were mild and transient in controlled clinical studies with various doses of candesartan cilexetil/hydrochlorothiazide (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg). The overall incidence of adverse events showed no association with age or gender.

In controlled clinical studies, discontinuation due to adverse events occurred in 2.3-3.3% and 2.7-4.3% of patients treated with candesartan cilexetil/hydrochlorothiazide and placebo, respectively. In studies to support the 16 mg / 12.5 mg strength, the incidence of serious adverse events observed with candesartan cilexetil/hydrochlorothiazide was 2.7% (71 out of 2582 patients). The incidence of serious adverse events was lower in the candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg dosage groups with the highest frequency of 0.8% (5 out of 664 patients) observed in the 32 mg / 25 mg group.

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.

In the double blind placebo controlled studies to support candesartan cilexetil/ hydrochlorothiazide 16 mg / 12.5 mg, the overall incidence of adverse events showed no association with age or gender. In these studies the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in ≥ 1% of patients, regardless of drug relationship (see Table 1).

Table 1 Adverse events reported with candesartan cilexetil/hydrochlorothiazide in ≥ 1% of patients regardless of causality in studies supporting the 16 mg / 12.5 mg strength

	Candesartan cilexetil/ hydrochlorothiazide (n=1025)	Candesartan cilexetil (n=749)	Hydrochloro-thiazide (n=603)	Placebo (n=526)
	%	%	%	%
Body as a Whole				
back pain	3.8	5.5	5.1	3.0
arthralgia	1.5	1.3	1.3	0.8
fatigue	1.4	1.2	1.7	1.0
abdominal pain	1.3	1.7	0.7	1.1
Urinary				
urinary tract infection	1.6	1.3	1.8	1.0
Digestive				
nausea	1.5	0.9	1.2	0.6
diarrhea	1.1	0.7	0.5	1.3
gastroenteritis	1.0	0.5	1.0	0.4
Cardiovascular				

tachycardia	1.3	0.9	1.2	0.8
ECG abnormal	1.2	1.2	0.3	0.8
edema peripheral	1.1	1.6	2.2	1.3
chest pain	1.0	0.7	1.0	0.6
Metabolic Disorders				
hyperuricemia	1.1	0.7	0.8	0.4
hyperglycemia	1.0	0.9	0.5	0.2
Nervous/Psychiatric				
headache	4.3	7.6	7.6	7.0
dizziness	3.1	3.9	2.0	1.5
inflicted injury	2.0	2.0	3.0	1.9
Respiratory				
upper respiratory tract infection	3.7	5.1	5.6	1.9
influenza-like symptoms	2.8	2.3	3.0	2.9
sinusitis	2.3	2.9	3.5	1.9
bronchitis	2.1	2.8	2.5	2.5
pharyngitis	1.4	0.9	1.0	1.7
cough	0.9	2.3	1.7	1.0
rhinitis	1.2	1.5	1.2	0.4

In double blind, controlled studies with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg, and 32 mg / 25 mg the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in ≥ 1% of patients, regardless of drug relationship (see Table 2).

Table 2 Adverse events reported with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg in ≥ 1% of patients regardless of causality

	Candesartan cilexetil/ hydrochlorothiazide (n=1873)		**Candesartan cilexetil (n=1188)**	**Hydrochloro-thiazide (n=540)**	**Placebo (n=163)**
	32 mg / 12.5 mg (n= 718)	**32 mg / 25 mg (n= 1155)**			
	%	**%**	**%**	**%**	**%**
Body as a Whole					
back pain	2.4	1.6	1.1	0.6	2.5
fatigue	1.1	0.9	0.8	0.4	2.5
arthralgia	0.6	1.1	0.6	1.1	1.8
Digestive					
diarrhea	1.1	0.4	0.7	0.4	1.8
Metabolic Disorders					

dyslipidaemia	3.3	2.5	1.9	0.4	0
Nervous/ Psychiatric					
dizziness	2.5	2.9	1.3	2.4	0.6
headache	2.4	2.0	5.1	7.6	7.4
Respiratory					
cough	1.4	0.7	0.6	1.3	1.2
nasopharyngitis	1.3	1.4	1.0	0.6	0
upper respiratory tract infection	1.3	0.3	1.7	3.5	5.5
bronchitis	1.1	0.9	1.0	1.3	1.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Candesartan cilexetil

The following adverse events were reported at an incidence of <1% in controlled clinical trials (in more than one patient, with higher frequency than placebo):

Body as a Whole: allergy, asthenia, pain, syncope.
Cardiovascular: angina pectoris, circulatory failure, flushing, hypotension, myocardial infarction, peripheral ischemia, thrombophlebitis.
Central and Peripheral Nervous System: hypertonia, hypoesthesia, paresthesia, vertigo.
Gastrointestinal: constipation, dyspepsia, dry mouth, toothache.
Hearing: tinnitus.
Metabolic and Nutritional: diabetes mellitus, hyperkalaemia, hyponatraemia.
Musculoskeletal: arthritis, arthropathy, myalgia, myopathy, skeletal pain, tendon disorder.
Blood: anemia, epistaxis.
Psychiatric: depression, impotence, neurosis.
Reproductive: menopausal symptoms.
Resistance Mechanism: otitis.
Respiratory: laryngitis.
Skin: eczema, pruritus, rash, skin disorder, sweating, (rarely) urticaria.
Urinary: abnormal urine, cystitis.
Vision: conjunctivitis.

There was no clear indication of dose-response relationship for any of the most common adverse events.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of candesartan cilexetil/hydrochlorothiazide.

Liver Function Tests: in controlled clinical trials, elevations of ALT (> 3 times the upper limit of normal) occurred in 0.9% of patients treated with candesartan cilexetil/hydrochlorothiazide compared to 0% of patients receiving placebo. Minor increases in serum AST have been observed in single patients receiving candesartan cilexetil/hydrochlorothiazide.

Serum Potassium, Sodium: a small decrease (mean decrease of 0.1 mmol/L) in serum potassium was observed in patients treated with candesartan cilexetil/hydrochlorothiazide but was rarely of clinical importance. Values of serum potassium below the predefined lower critical limit were recorded in 0.6% of patients in controlled clinical trials with candesartan cilexetil/hydrochlorothiazide. An increase in serum potassium has rarely been observed with candesartan cilexetil/hydrochlorothiazide. A decrease in sodium has been observed with candesartan cilexetil/hydrochlorothiazide.

Hemoglobin and Hematocrit: small decreases in hemoglobin were observed in patients treated with candesartan cilexetil/hydrochlorothiazide but were rarely of clinical importance. Values of hemoglobin below the predefined critical limit were recorded in 0.9% of patients in controlled clinical trials with candesartan cilexetil/hydrochlorothiazide.

Blood glucose: in controlled clinical trials, elevations of blood glucose occurred in 1.0% of patients treated with candesartan cilexetil/hydrochlorothiazide compared to 0.2% of patients receiving placebo.

Hyperuricemia: increases in serum uric acid were found in 1.1% of patients treated with candesartan cilexetil/hydrochlorothiazide and 0.4% of patients treated with placebo.

Creatinine, Urea: An increase in creatinine and urea has been observed with candesartan cilexetil/hydrochlorothiazide.

Post-Market Adverse Drug Reactions

Candesartan cilexetil

Angioedema, (involving swelling of the face, lips and/or tongue) has been reported rarely in patients treated with candesartan cilexetil.

In other post-marketing experience, renal impairment, including renal failure in susceptible patients, has been observed (see WARNINGS AND PRECAUTIONS, Renal, – Renal Impairment for definition of susceptible patients).

Very rare cases of abnormal hepatic function or hepatitis have also been reported.

Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of leukopenia, neutropenia and agranulocytosis.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide

Potentially serious clinical adverse events have been reported to occur with hydrochlorothiazide, such as: jaundice (intrahepatic cholestatic jaundice), pancreatitis, leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, haemolytic anemia, photosensitivity reactions, necrotising angitis (vasculitis), toxic epidermal necrolysis, anaphylactic reactions, respiratory distress (including pneumonitis and pulmonary edema), hypokalemia, renal dysfunction, interstitial nephritis, acute myopia, acute angle-closure glaucoma, systemic lupus erythematosus and cutaneous lupus erythematosus.

DRUG INTERACTIONS

Overview

In vitro studies indicate that cytochrome P450 isoenzyme CYP 2C9 is involved in the biotransformation of candesartan to its inactive metabolite. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 3 Established or Potential Drug-Drug Interactions

Proper Name	Ref.	Effect	Clinical Comment
Agents Increasing Serum Potassium	T	Candesartan cilexetil decreases the production of aldosterone.	Potassium-sparing diuretics or potassium supplements or other drugs that may increase serum potassium levels (e.g. heparin, co-trimoxazole) should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Proper Name	Ref.	Effect	Clinical Comment
			Concomitant thiazide diuretic use, or switching to candesartan cilexetil/hydrochlorothiazide may attenuate any effect that candesartan cilexetil may have on serum potassium.
Alcohol, barbiturates or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amantadine	T	Co-administration of thiazide diuretics may increase the risk of adverse effects caused by amantadine.	Monitor the patient closely and adjust the dosage of either medication as required.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Anti-cholinergic agents (e.g., atropine, biperiden, domperidone and metoclopramide)	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of candesartan cilexetil/hydrochlorothiazide may be required.
Antidiabetic agents (e.g. insulin or oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors).	Dose adjustments of other concomitantly taken antihypertensive drugs may be required.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematologic status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, cholestyramine	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%.	Give candesartan cilexetil/hydrochlorothiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a

Proper Name	Ref.	Effect	Clinical Comment
		Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	consistent sequence of administration. Monitor blood pressure, and increase dose of candesartan cilexetil/hydrochlorothiazide, if necessary.
Calcium and Vitamin D supplements	C	Administration of thiazide with vitamin D, or with calcium salts may potentiate the rise in serum calcium. Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with thiazide diuretics.	Monitor serum potassium and adjust medications, as required.
Cyclosporine	T	May increase the risk of hyperuricemia and gout type complications.	Serum uric acid levels should be closely monitored and medications adjusted, as required.
Diazoxide	C	Co-administration of thiazide diuretics enhances the hyperglycemic effect of diazoxide.	Blood glucose levels should be monitored and dose adjustment of insulin or antidiabetics may be required in diabetic patients.
Digoxin	CT	Combination treatment with candesartan cilexetil and digoxin in healthy volunteers had no effect on AUC or C_{max} values for digoxin compared to digoxin alone. Similarly, combination treatment had no effect on AUC or C_{max} values for candesartan compared to candesartan cilexetil alone. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of candesartan cilexetil/hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or candesartan cilexetil/hydrochlorothiazide, as required.

Proper Name	Ref.	Effect	Clinical Comment
Diuretics	CT	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with candesartan cilexetil.	The possibility of symptomatic hypotension with the use of candesartan cilexetil can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of candesartan cilexetil (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interactions of clinical significance have been identified with thiazide diuretics. When candesartan cilexetil/hydrochlorothiazide is used, other diuretics are, as a rule, unnecessary.
Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	CT	Clinical trial data has shown that dual blockade of the RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.	Dual blockade of the RAS with ARBs or ACEIs and aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment (see CONTRAINDICATIONS). The combined use of ARBs, ACEIs or aliskiren-containing drugs is generally not recommended (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)).
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Use of candesartan cilexetil/hydrochlorothiazide in patients with gout is contraindicated (see CONTRAINDICATIONS).
Lithium Salts	CT	As with other drugs which eliminate sodium, lithium clearance may be reduced. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of candesartan cilexetil/hydrochlorothiazide with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor closely. Serum lithium levels should be monitored carefully if lithium salts are to be administered.

Proper Name	Ref.	Effect	Clinical Comment
Methyldopa	C	There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.	Monitor for symptoms of anemia. If anemia is confirmed, tests should be done for hemolysis. If hemolytic anemia is present, candesartan cilexetil/hydrochlorothiazide should be discontinued.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Attenuation of the antihypertensive effect may occur when simultaneously administering ARBs and NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid and non-selective NSAIDs). As with ACE inhibitors, concomitant use of ARBs and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.	When candesartan cilexetil/hydrochlorothiazide and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. The combination of ARBs and NSAIDs should be administered with caution, especially in older patients and in volume depleted patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter. If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required. Patients with heart failure may be at particular risk.
Pressor Amines (e.g., norepinephrine)	T	In the presence of thiazide diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.	Monitor and consider dose adjustments if required.
Selective Serotonin Reuptake Inhibitors (SSRIs, e.g., citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurarine	C	Thiazide drugs may increase the responsiveness of some nondepolarizing skeletal muscle relaxants, such as curare derivatives.	
Topiramate	CT	Additive hypokalemia.	Monitor serum potassium and

Proper Name	Ref.	Effect	Clinical Comment
		Possible thiazide-induced increase in topiramate serum concentrations.	topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.
Warfarin	CT	When candesartan cilexetil was administered at 16 mg once daily under steady state conditions, no pharmacodynamic effect on prothrombin time was demonstrated in subjects stabilized on warfarin.	
Other	CT	No significant drug interactions have been reported with glyburide, nifedipine or oral contraceptives co-administered with candesartan cilexetil to healthy volunteers.	

Legend: C= Case Study; RCS=Retrospective Cohort Study; CT= Clinical Trial; T= Theoretical

Drug-Food Interactions

Mylan-Candesartan HCTZ may be taken with or without food (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) must be individualized. The fixed combination is not for initial therapy. The dose of Mylan-Candesartan HCTZ should be determined by titration of the individual components.

Recommended Dose and Dosage Adjustment

Once the patient has been stabilized on the individual components, one Mylan-Candesartan HCTZ 16 mg / 12.5 mg, 32 mg / 12.5 mg or 32 mg / 25 mg tablet once daily may be taken if the doses on which the patient was stabilized are the same as those in the fixed combination (see INDICATIONS AND CLINICAL USE).

Initiation of therapy requires consideration of recent antihypertensive treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors.

Mylan-Candesartan HCTZ should be taken once daily, at approximately the same time each day, with or without food.

Candesartan cilexetil Monotherapy

The recommended initial dose of candesartan cilexetil is 16 mg, once daily. Total daily doses of candesartan cilexetil should range from 8 to 32 mg. Doses higher than 32 mg do not appear to have a greater effect on blood pressure reduction, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks and the maximal blood pressure reduction is generally obtained within 4 weeks. For patients with possible depletion of intravascular volume (e.g. patients treated with diuretics, particularly those with impaired renal function) consideration should be given to administration of a lower dose. If blood pressure is not controlled by candesartan cilexetil alone, a thiazide diuretic may be added (see DRUG INTERACTIONS, Drug-Drug Interactions, Diuretics).

Concomitant Diuretic Therapy

In patients receiving diuretics, candesartan cilexetil therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy.

Whenever possible, all diuretics should be discontinued two to three days prior to the administration of candesartan cilexetil, to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension). If this is not possible because of the patient's condition, candesartan cilexetil should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

As a rule, concomitant diuretic therapy is not necessary when Mylan-Candesartan HCTZ is used.

Dosing Considerations in Special Populations

Hepatic Impairment

Patients with hepatic impairment: Dose titration is recommended in patients with mild to moderate chronic liver disease.

Mylan-Candesartan HCTZ is contraindicated in patients with severe hepatic impairment and/or cholestasis (see CONTRAINDICATIONS).

Renal Impairment

In patients with mild to moderate renal impairment (ie, creatinine clearance between 30-80 mL/min/1.73m^2 BSA), a dose titration is recommended.

Mylan-Candesartan HCTZ is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2 BSA) (see CONTRAINDICATIONS).

Geriatrics (> 65 years of age)
No dose adjustment of Mylan-Candesartan HCTZ is necessary for elderly patients. As greater sensitivity of some older patients cannot be ruled out, appropriate caution is recommended (see WARNINGS AND PRECAUTIONS, Geriatrics).

Pediatrics (< 18 years of age)
The safety and efficacy of candesartan cilexetil/hydrochlorothiazide have not been established in children.

Mylan-Candesartan HCTZ is contraindicated in children aged < 1 year (see CONTRAINDICATIONS).

Missed Dose
If a patient misses a dose of Mylan-Candesartan HCTZ and remembers within 12 hours, the patient should take the dose as soon as possible and then go back to the regular schedule. If it is more than 12 hours after the patient remembers, they should not take the missed dose; the next dose should be taken on time.

A double dose of Mylan-Candesartan HCTZ should never be taken to make up for a missed dose.

OVERDOSAGE

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

No specific information is available on the treatment of overdosage with candesartan cilexetil/hydrochlorothiazide. Treatment is symptomatic and supportive.

Candesartan cilexetil

Limited data are available in regard to overdosage of candesartan cilexetil in humans. The most likely manifestations of overdosage would be hypotension, dizziness and tachycardia; bradycardia could occur from reflex parasympathetic (vagal) stimulation. Thirst, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed. If symptomatic hypotension should occur, supportive treatment should be instituted and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic drugs may also be administered if the above-mentioned measures are not sufficient. In case reports detailing overdosage (≤ 672 mg candesartan cilexetil) patient recovery was uneventful.

Candesartan cilexetil is not removed from the plasma by hemodialysis.

Hydrochlorothiazide

The most common symptoms observed from overdosage of hydrochlorothiazide are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) combines the actions of candesartan cilexetil, an angiotensin II AT_1 receptor blocker, and that of a thiazide diuretic, hydrochlorothiazide.

Candesartan cilexetil

Candesartan cilexetil antagonizes the action of angiotensin II by blocking the angiotensin type one (AT_1) receptor. Angiotensin II is the primary vasoactive hormone of the RAAS with effects that include vasoconstriction, stimulation of aldosterone secretion, and renal reabsorption of sodium.

Candesartan cilexetil, a prodrug, is rapidly converted to the active drug, candesartan, during absorption from the gastrointestinal tract.

Candesartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There are also AT_2 receptors found in many tissues, but they play no known role in cardiovascular homeostasis to date. Candesartan has a much greater affinity (> 10,000-fold) for the AT_1 receptor than for the AT_2 receptor. The strong bond between candesartan and the AT_1 receptor is a result of tight binding to and slow dissociation from the receptor.

Candesartan does not inhibit ACE, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It inhibits the active reabsorption of sodium, mainly in the distal kidney tubules, and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed

to a greater extent. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

Pharmacodynamics

Candesartan cilexetil

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing of 8 mg candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak (4-8 hours after dosing) with approximately 50% inhibition persisting at 24 hours. Plasma concentrations of angiotensin I, angiotensin II, and plasma renin activity, increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. A decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients.

Hydrochlorothiazide

Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Pharmacokinetics

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product.

Candesartan cilexetil

Absorption: Following oral administration of candesartan cilexetil as a tablet, the absolute bioavailability of candesartan is estimated to be approximately 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3-4 hours. Food does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Distribution: The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan does cross the blood- brain barrier. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Metabolism: Candesartan cilexetil is rapidly and completely bioactivated to candesartan by ester hydrolysis during absorption from the gastrointestinal tract. It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. *In vitro* studies indicate that cytochrome P450 isoenzyme CYP 2C9 is involved in the biotransformation of candesartan to its inactive metabolite. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Excretion: Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. Candesartan is mainly excreted unchanged in urine and feces (via bile). When candesartan cilexetil is administered orally, about 26% of the dose is excreted as candesartan in urine. Following an oral dose of ^{14}C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous (iv) dose of ^{14}C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear, for oral doses ≤ 32 mg. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Hydrochlorothiazide

Absorption: hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant food intake increases the absorption by approximately 15%.

Distribution: the bioavailability may decrease in patients with cardiac failure and pronounced edema. The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 L/kg.

Excretion: hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal $t_{½}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (8 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in the elderly and in patients with renal failure or chronic heart failure.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations and Conditions

Geriatrics: The plasma concentration of candesartan was higher in the elderly (≥ 65 years old) (C_{max} was approximately 50% higher and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration.

Gender: No gender-related differences in the pharmacokinetics of candesartan have been observed.

Hepatic Insufficiency:
Mild to moderate hepatic impairment: There was an increase in the AUC of candesartan of approximately 20%. There was no drug accumulation in plasma in these patients.

Moderate to severe hepatic impairment: C_{max} and AUC increased up to 5x in a very small group administered a single dose of 16 mg candesartan (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Renal Insufficiency:
Mild to moderate renal impairment (Cl_{creat} 31-60 mL/min/1.73m^2): C_{max} and AUC of candesartan increased by 40-60% and 50-90%, respectively, but $t_{½}$ was not altered, compared to patients with normal renal function (Cl_{creat} > 60 mL/min/1.73m^2) during repeated dosing. There was no drug accumulation in plasma.

Severe renal impairment (Cl_{creat} 15-30 mL/min/1.73m^2): The increases in C_{max} and AUC were 40-60% and 110%, respectively. The terminal $t_{½}$ of candesartan was approximately 2x in patients with severe renal impairment, and these changes resulted in some accumulation in plasma.

Patients undergoing hemodialysis: The pharmacokinetics of candesartan were similar to those in patients with severe renal impairment (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Renal Impairment).

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) is available in tablets of 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg.

Composition

Each tablet contains candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg.

Each tablet also contains the following non-medicinal ingredients: carmellose calcium, glyceryl monostearate, hydroxypropylcellulose, iron oxide red (16 mg/12.5 mg and 32 mg/25 mg strengths only), iron oxide yellow, lactose monohydrate, magnesium stearate and maize starch.

Packaging

Mylan-Candesartan HCTZ 16 mg / 12.5 mg tablets are peach, mottled, oval biconvex tablets debossed with "M" on left side of the break line on one side and "CH" and "5" on either side of the break line on the other side, available in Coldform blister packs of 30 tablets (2 x 15's), PVC/Aclar Blister packs of 30 tablets (15 x 2) and in HDPE bottles containing 100 tablets.

Mylan-Candesartan HCTZ 32 mg / 12.5 mg tablets are: Yellow coloured, mottled, oval biconvex tablets debossed with "M" on left side of the break line and "CH6" on right side of the break line on one side and scored on the other side. Available in HDPE bottles containing 100 tablets.

Mylan-Candesartan HCTZ 32 mg / 25 mg tablets are: Pink coloured, mottled, oval biconvex tablets debossed with "M" on left side of the break line and "CH7" on right side of the break line on one side and score on the other side. Available in HDPE bottles containing 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance – Candesartan cilexetil

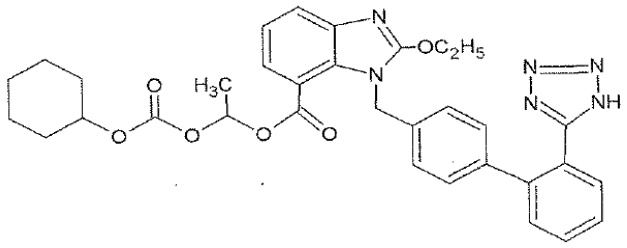
Proper Name: candesartan cilexetil

Chemical Name: (±)2-Ethoxy-1-[[2'-(1*H*-tetrazol-5-yl)[1, 1'- biphenyl]-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid-1[[(cyclohexyloxy)carbonyl]oxy]ethyl ester

Molecular Formula and $C_{33}H_{34}N_6O_6$

Molecular Mass 610.66 g/mol

Structural Formula



Physiochemical Properties

Description:
Candesartan cilexetil is a white to off-white powder.

Melting Point:
161.2 – 164.8°C

Solubilities in common solvents:

Solvent	Quantity dissolved at 25°C (mg/mL)	Descriptive Term (as defined in the USP)
Ethanol	11.0	Sparingly soluble
Ethylacetate	20.0	Sparingly soluble
Water	<0.1 mg/mL	Practically insoluble
Dimethylformamide	930.0	Freely soluble
Dimethylsulfoxide	595.0	Freely soluble
Chloroform	755.0	Freely soluble
Acetone	51.0	Soluble

Quantitative aqueous pH solubility profile:

Buffer pH	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
1.2	<0.1 mg/mL	Practically insoluble
6.0	<0.1 mg/mL	Practically insoluble
8.0	<0.1 mg/mL	Practically insoluble

Partition Coefficient:

pH of Aqueous Layer	Partition Coefficient (K at 20°C)	
	Ethyl Ether	1-Octanol
1.1	>1000	>1000
6.9	>1000	>1000
8.9	141	>1000

$$K = \frac{\text{Concentration of Candesartan Cilexetil in the organic layer}}{\text{Concentration of Candesartan Cilexetil in the aqueous layer}}$$

Drug Substance – Hydrochlorothiazide

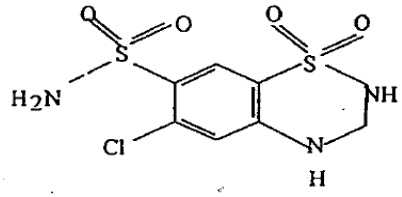
Proper Name: hydrochlorothiazide
Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide1,1-dioxide

Molecular Formula and Molecular Mass

$C_7H_8ClN_3O_4S_2$

297.7 g/mol

Structural Formula



Physiochemical Properties

Description:
Hydrochlorothiazide is a white, or almost white, crystalline powder.

Melting Point:
about 270°C

Solubilities in common solvents:

Solvent	Descriptive Term (Solubility as per Ph.Eur monograph)
Water	Very slightly soluble
Acetone	Soluble
Ethanol (96%)	Sparingly soluble

Quantitative aqueous pH solubility profile (at 37ºC):

Buffer pH	Solubility (mg/mL)	Descriptive Term (as defined in the USP)
0.1N HCl	0.099	Practically insoluble
pH 45 acetate buffer	0.097	Practically insoluble
pH 6.8 phosphate buffer	0.095	Practically insoluble

Partition Coefficient: Hydrochlorothiazide

	Ionization constant (pKa at 25°C)
pH of Aqueous Layer	n-Octanol
1.06	1.94
3.00	0.866
7.40	0.855

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, randomized, single oral dose, balanced, two-way crossover bioequivalence study to compare Mylan-Candesartan HCTZ (candesartan cilexetil and hydrochlorothiazide 16 mg/12.5 mg) tablets of Mylan Pharmaceuticals ULC, with Atacand® Plus (candesartan cilexetil and hydrochlorothiazide 16 mg/12.5 mg) tablets of AstraZeneca Canada Inc. was conducted in 43 and 27 healthy, Adult, Asian Indian Male subjects for candesartan cilexetil and hydrochlorothiazide, respectively, under fasting conditions.

A Summary of the results are presented in the following table.

16 mg / 12.5 mg Tablets

For Candesartan:

Candesartan (1 x16 mg/12.5 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	(%) Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	1144.20 1235.90 (38.92)	1314.63 1387.66 (35.12)	87.04	(80.38, 94.25)
AUC_I (ng.h/mL)	1255.05 1343.97 (36.69)	1411.13 1476.33 (32.31)	88.94	(82.92, 95.39)
C_{max} (ng/mL)	121.70 131.65 (39.49)	136.05 145.40 (39.48)	89.45	(82.20, 97.35)
T_{max} § (h)	3.50 (2.00, 7.00)	3.50 (2.50, 7.00)		
$T_{½}$ € (h)	9.03 (38.47)	8.365 (32.54)		

* Mylan-Candesartan HCTZ 16 mg/12.5 mg tablets (Mylan Pharmaceuticals ULC)
† ATACAND® PLUS 16 mg/12.5 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as Median (range) only
€ Expressed as arithmetic mean (CV %) only

For Hydrochlorothiazide:

Hydrochlorothiazide (1 x16 mg/12.5 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	559.00 588.36 (34.27)	520.50 530.68 (19.96)	107.40	(99.12 - 116.36)
AUC_I (ng.h/mL)	582.71 611.96 (33.71)	548.68 560.54 (21.97)	106.20	(98.13 - 114.94)
C_{max} (ng/mL)	78.45 83.46 (35.79)	71.29 73.96 (27.07)	110.04	(100.25 - 120.78)
T_{max} § (h)	2.00 (1.00, 3.50)	2.50 (1.00, 3.50)		
$T_{½}$ € (h)	9.64 (11.76)	9.66 (24.29)		

* Mylan-Candesartan HCTZ 16 mg/12.5 mg tablets (Mylan Pharmaceuticals ULC)
† ATACAND® PLUS 16 mg/12.5 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as Median (range) only
€ Expressed as arithmetic mean (CV %) only

32 mg / 12.5 mg Tablets

A single-dose, randomized, balanced, double-blind, two-treatment, two-sequence, two-period, two-way crossover, bioequivalence study comparing 1 x 32 mg/12.5 mg Mylan-Candesartan HCTZ (Candesartan cilexetil /hydrochlorothiazide) tablet (Mylan Pharmaceuticals ULC) and 1 x 32 mg/12.5 mg ATACAND® PLUS 32 mg/12.5 mg (Candesartan cilexetil/hydrochlorothiazide) tablet (AstraZeneca Canada Inc.) was performed in healthy, adult, male subjects (n = 30) under fasting conditions.

A summary of the results are presented in the following tables.

For Candesartan:

Candesartan (1 x 32 mg/12.5 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	4538.35 4758.37 (30.8)	4249.79 4470.24 (32.4)	106.8	97.60-116.84
AUC_I (ng.h/mL)	4671.96 4905.82 (31.3)	4387.15 4619.18 (32.5)	106.5	97.15-116.73
C_{max} (ng/mL)	400.34 429.14 (43.8)	350.28 381.42 (43.7)	114.3	101.66 – 128.50
T_{max} § (h)	3.50 (1.50-8.00)	4.50 (1.50-8.00)		

Candesartan (1 x 32 mg/12.5 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
$T_{½}$ € (h)	9.3 (23.3)	9.4 (27.2)		

* Mylan-Candesartan HCTZ 32 mg/12.5 mg tablets (Mylan Pharmaceuticals ULC)
† ATACAND® PLUS 32 mg/12.5 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

For Hydrochlorothiazide:

Hydrochlorothiazide (1 x 32 mg/12.5 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	668.45 684.39 (21.3)	662.96 682.15 (22.3)	100.8	95.42-106.54
AUC_I (ng.h/mL)	711.76 727.97 (20.7)	710.29 727.92 (20.9)	100.2	94.95-105.76
C_{max} (ng/mL)	93.77 96.50 (25.0)	92.79 96.07 (25.0)	101.1	95.39 – 107.07
T_{max} § (h)	1.50 (1.00-3.50)	1.50 (1.00-4.50)		
$T_{½}$ € (h)	9.9 (20.2)	10.2 (15.5)		

* Mylan-Candesartan HCTZ 32/12.5 mg tablets (Mylan Pharmaceuticals ULC)
† Atacand® PLUS 32 mg/12.5 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

32 mg / 25 mg Tablets

A single-dose, randomized, balanced, double-blind, two-treatment, two-sequence, two-period, two-way crossover, bioequivalence study comparing 1 x 32 mg/25 mg Mylan-Candesartan HCTZ (Candesartan cilexetil/hydrochlorothiazide) tablet (Mylan Pharmaceuticals ULC) and 1 x 32 mg/25 mg ATACAND® PLUS 32 mg/25 mg (Candesartan cilexetil/hydrochlorothiazide) tablet (AstraZeneca Canada Inc.) was performed in healthy, adult, male subjects (n = 29) under fasting conditions.

A summary of the results are presented in the following tables.

For Candesartan:

Candesartan (1 x 32 mg/25 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	2179.63 2302.42 (34.8)	2106.84 2203.98 (30.7)	103.5	97.05-110.28
AUC_I (ng.h/mL)	2227.19 (2355.19 (35.1)	2159.45 2259.18 (30.7)	103.1	96.84-109.85
C_{max} (ng/mL)	206.84 220.01 (35.7)	189.17 202.79 (38.0)	109.3	99.88 – 119.69
T_{max} § (h)	4.50 (1.50-8.00)	4.00 (1.50-8.00)		
$T_{½}$ € (h)	8.2 (21.2)	8.2 (21.8)		

* Mylan-Candesartan HCTZ 32/25 mg tablets (Mylan Pharmaceuticals ULC)
† Atacand® PLUS 32 mg/25 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

For Hydrochlorothiazide:

Hydrochlorothiazide (1 x 32 mg/25 mg candesartan cilexetil/hydrochlorothiazide tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference †	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	1225.28 1264.12 (24.7)	1217.49 1245.24 (20.9)	100.6	96.65-104.80
AUC_I (ng.h/mL)	1273.50 1312.27 (24.3)	1268.00 1293.64 (20.0)	100.4	96.51-104.51
C_{max} (ng/mL)	168.03 174.43 (27.4)	171.09 178.87 (32.2)	98.2	99.38 – 119.09
T_{max} § (h)	2.00 (1.00-4.50)	2.00 (1.00-4.00)		
$T_{½}$ € (h)	9.3(16.8)	9.7(17.1)		

* Mylan-Candesartan HCTZ 32/25 mg tablets (Mylan Pharmaceuticals ULC)
† Atacand® PLUS 32 mg/25 mg tablets (manufactured by AstraZeneca Canada Inc.) were purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

Candesartan cilexetil

In hypertension, candesartan cilexetil causes a dose-dependent reduction in arterial blood pressure (BP). Systemic peripheral resistance is decreased, while heart rate, stroke volume and cardiac output are not significantly affected. No first-dose hypotension was observed during controlled clinical trials with candesartan cilexetil.

Most of the antihypertensive effect was seen within 2 weeks of initial dosing, and the full effect in 4 weeks. With once-daily dosing, BP effect was maintained over
24 hours, with trough to peak ratios of BP effect generally > 80%. Candesartan cilexetil had an additional BP lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients < 65 and ≥ 65 years. Candesartan was effective in reducing BP regardless of race, although the effect was somewhat less in Black patients (usually a low-renin population) than in Caucasian patients.

In long-term studies of ≤ 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained and there was no rebound after abrupt withdrawal.

Candesartan cilexetil also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension, and microalbuminuria. In a 12-week study of 161 mildly hypertensive patients with type II diabetes mellitus, candesartan cilexetil 8 - 16 mg had no effect on mean HbA1c.

Comparative Effects
The antihypertensive efficacy of candesartan cilexetil and losartan potassium have been compared at their approved once daily maximum doses, 32 mg and 100 mg, respectively, in patients with mild to moderate essential hypertension. Candesartan cilexetil lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium when measured at the time of either peak or trough effect. Both agents were well tolerated.

Candesartan cilexetil/hydrochlorothiazide

Candesartan cilexetil and hydrochlorothiazide have additive antihypertensive effects. After administration of a single dose of candesartan cilexetil/hydrochlorothiazide in hypertensive patients, onset of the antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment. Candesartan cilexetil/hydrochlorothiazide given once daily provides effective and smooth dose-dependent blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval and without reflex increase in heart rate. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

Randomized placebo controlled studies with the combination of candesartan cilexetil and hydrochlorothiazide 32 mg / 12.5 mg or 32 mg / 25 mg once daily demonstrated a dose-dependent blood pressure lowering effect of candesartan cilexetil/hydrochlorothiazide. The

combination produced a statistically significant effect larger than candesartan cilexetil or hydrochlorothiazide monotherapy. The proportion of patients with controlled blood pressure was larger and the effect of the combination was dose-related.

Candesartan cilexetil/hydrochlorothiazide is similarly effective in patients irrespective of age and gender.

DETAILED PHARMACOLOGY

Animal Pharmacology

In an *in vitro* assay system, hydrochlorothiazide at 10^{-5} M did not affect the inhibition of binding of [^{125}I]AII to the AII receptor by candesartan.

HCTZ at 10 mg/kg/day had no effect on blood pressure in conscious spontaneously hypertensive rats. HCTZ combined with 0.1 or 1 mg/kg of candesartan cilexetil, synergistically intensified the reduction in blood pressure induced by candesartan cilexetil.

TOXICOLOGY

Acute Toxicity

Table 6 Acute Toxicity

Route	Species	Sex	LD_{50} (mg/kg) values
oral gavage	rat	Male Female	>2000 candesartan cilexetil & >1000 HCTZ

Chronic Toxicity

The toxic potential of candesartan cilexetil was evaluated in a series of repeated-dose oral toxicity studies of ≤13 weeks in rats and dogs. The no toxic effect dose level for candesartan cilexetil/hydrochlorothiazide was 1/10 mg/kg/day in rats.

Table 7 Toxicity Upon Repeated Oral Administration

Species/ Strain	No. Of Animals per Group	Duration and Route of Adminis-tration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Rat / Fischer 344/DuCrj	10M + 10F	4 weeks dietary	0/0 0/10 300/0 3/10 30/10 300/10	No deaths, and no treatment related abnormalities in clinical signs, urine chemistry, or gross pathology, or upon urinanalysis or ophthalmic examinations. Decr. in body weight, food consumption, heart weight and osmolality and increase in incidence of basophilic renal tubules, hypertrophy of juxtaglomerular cells for grps 300/0 and 300/10. Grps 300/0, 30/10 and 300/10 had an incr. in urine output, water intake, urea nitrogen, total chol. and atrophy of zona glomerulosa and a decr. in osmolality, erythrocytes, hematocrit and hemoglobin conc. and triglycerides. Grps 30/10 and 300/10 had an incr. in creatinine, ALP, LAP and inorganic phosphorus. M in grps 300/0 and 30/10 had an incr. in potassium as well as M and F in grp 300/10. F in grp 3/10 had an incr. in urine output, water intake, ALP, LAP and atrophy of the zona glomerulosa. F in grp 0/10 and 3/10 had a decr. in chloride.
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 1/10 10/10 100/10	No deaths, and no abnormal signs. No toxicokinetic interactions occurred btw candesartan cilexetil and HCTZ. Grps 10/10 and 100/10 had an increase in basophilia of the renal tubules, calcification in the renal papilla, blood urea nitrogen, inorganic phosphorus and a decr. in calcium, total protein red blood cells, hemoglobin and hematocrit. The 100/10 grp had atrophy of the zona glomerulosa, urinary casts, white kidney patches, and an incr. in creatinine, and corpuscular volume.
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 0/30 100/0 100/30	No deaths occurred and no abnormal signs. Toxic effects were seen in the 100/30 grp which included basophilic renal tubules and erosion/regeneration of the stomach. Decr. in body weight, urine osmolality and increases in water intake, urine volume, serum blood nitrogen and pathological changes noted above increased with concurrent administration. The 100/30 grp had an incr. in serum creatinine and inorganic phosphorus as well as shortening of prothrombin time and activated partial thromboplastin time.

Species/ Strain	No. Of Animals per Group	Duration and Route of Adminis-tration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Beagle	3M + 3F	4 weeks dietary	0/0 0/10 4/0 20/0 100/0 4/10 20/10 100/10	2 M were sacrificed after the 11th and 24th dose and 3 F died: 2 after the 10th dose and 1 after the 14th dose in the 100/10 (N=6) grp due to decreased locomotor activity, lack of food consumption and increase in plasma urea nitrogen concentration and creatinine. Increases in regeneration of renal tubules, hypertrophy of the juxtaglomerular cells, erosion or ulcer of the stomach were noted in most of the 100/10 grp and in some animals of the 20/10 group. Other abnormalities were decreases in osmolality, reticulocytes, chloride and potassium and increases in urea nitrogen, calcium, inorganic potassium, creatinine, erthyrocytes, hematocrit and hemoglobin which were observed in various groups other than the control.
Beagle	3M + 3F	13 weeks dietary	0/0 0.8/10 4/10 20/10	2 F were sacrificed after the 31st dose and 38th dose in the 20/10 grp due to a decr. in movement and food consumption, hypothermia, paleness of conjuctival and oral mucosa and constipation. These F had an incr. in serum urea nitrogen, creatinine, inorganic phosphates and a decr. in sodium and chloride. The kidneys had tubular dilatation, severe regeneration of renal tubules, hypertrophy of juxtaglomerular cells and vacuolization and calcification in papilla. The stomach had erosion, mucosal hemorrhage and calcification and glands demonstrated atrophy. Decr. in urinary osmotic pressure for grp 20/10 and F of grps 0.8/10 and 4/10 as well as an incr. in sodium content for the latter. All other animals sacrificed on schedule showed no treatment change except for histological changes to kidneys.
Beagle	3M + 3F	13 weeks dietary	0/0 4/0 0/30 4/30	Treatment related deaths or severe toxic signs or symptoms did not occur in any animal. Hypertrophy of the juxtaglomerular cells occurred in the 4/0 and 4/30 animals. Increased urine vol. and decr. serum potassium occurred in the 0/30 and 4/30 grps.

Reproductive and Developmental Studies
Reproductive studies were performed in rats, mice and rabbits. In rats, effects upon the maternal as well as upon the fetal body weight were recorded at 100/10 mg/kg/day and a minor skeletal effect was recorded upon the fetuses at 30/10 mg/kg/day with candesartan cilexetil/hydrochlorothiazide. The no observed adverse effect dose level in rats was 10/10 mg/kg of candesartan cilexetil and hydrochlorothiazide combination. The maternal toxicity was similar after monotherapy and the combination treatment. In mice, no maternal or fetal effects were seen at doses of up to 1000/10 mg/kg/day. In rabbits maternal toxicity with abortions and deaths was seen with doses from 1/10 mg/kg. The addition of hydrochlorothiazide did not significantly affect the outcome of the fetal development studies in any of the three species tested.

Effects on the development of the kidneys
Animal studies with candesartan cilexetil have demonstrated late fetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the RAAS. The RAAS plays a critical role in kidney development. RAAS blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the RAAS, such as candesartan cilexetil, can alter normal renal development. Therefore, Mylan-Candesartan HCTZ is contraindicated in children <1 year old (see CONTRAINDICATIONS).

Mutagenicity
The studies performed show that the 1:2 mixture of candesartan cilexetil and hydrochlorothiazide is devoid of genotoxic activity in a range of *in vitro* studies in bacteria and in *in vivo* studies. These studies showed that candesartan cilexetil did not have a synergistic mutagenic effect when administered with hydrochlorothiazide. Taking into consideration all the studies conducted on the components and the combination it is concluded that the probability that the combination of candesartan cilexetil and hydrochlorothiazide being genotoxic to humans is extremely low.

Carcinogenicity
No carcinogenicity studies were carried out with the candesartan cilexetil/hydrochlorothiazide combination.

The carcinogenic potential of candesartan cilexetil was studied in rats after administration in the diet for 24 months. Dose levels were 100, 300 and 1000 mg/kg/day (50 male and 50 female rats per group). No alteration in tumour profile was observed. A 2-year oral gavage study of candesartan cilexetil in mice was performed at daily dosages of 3, 10, 30 and 100 mg/kg/day. There was no alteration in the tumour profile.

There is no evidence that either candesartan cilexetil or hydrochlorothiazide are carcinogenic.

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ATACAND® PLUS, AstraZeneca Canada Inc., Product Monograph dated: February 19, 2016, Control No. 187943.

PART III: CONSUMER INFORMATION

[Pr]Mylan-Candesartan HCTZ

Candesartan Cilexetil/Hydrochlorothiazide Tablets

16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg

This leaflet is part III of a three-part "Product Monograph" published when Mylan-Candesartan HCTZ (candesartan cilexetil/hydrochlorothiazide) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Mylan-Candesartan HCTZ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Mylan-Candesartan HCTZ lowers high blood pressure.

What it does:
Mylan-Candesartan HCTZ contains a combination of 2 drugs, candesartan cilexetil and hydrochlorothiazide:

- Candesartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in **"-SARTAN"**. It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking Mylan-Candesartan HCTZ regularly even if you feel fine.

When it should not be used:
Do not take Mylan-Candesartan HCTZ if you:

- Are allergic to candesartan cilexetil, hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Have severe liver disease.
- Have severe kidney disease.
- Are allergic to any sulphonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE".
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat or sudden difficulty breathing or swallowing to any ARB (any drug in the same class as candesartan cilexetil). Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have difficulty urinating or produce no urine.
- Are pregnant or intend to become pregnant. Taking Mylan-Candesartan HCTZ during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. Mylan-Candesartan HCTZ passes into breast milk.
- Are less than 1 year old.
- Have gout.
- Have one of the following rare hereditary diseases:
  - o Galactose intolerance
  - o Lapp lactase deficiency
  - o Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in Mylan-Candesartan HCTZ.

What the medicinal ingredients are:
Candesartan cilexetil and hydrochlorothiazide.

What the non-medicinal ingredients are:
Most medicines contain more ingredients than just the active drug. These ingredients are needed to keep medicines in a form that you can swallow. Check with your doctor if you think you might be allergic to any of the following items (listed in alphabetical order): carmellose calcium, glyceryl monostearate, hydroxypropylcellulose, iron oxide red (16 mg/12.5 mg and 32 mg/25 mg strengths only), iron oxide yellow, lactose monohydrate, magnesium stearate and maize starch.

What dosage forms it comes in:
Mylan-Candesartan HCTZ is available as 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy
Mylan-Candesartan HCTZ should not be used during pregnancy. If you discover that you are pregnant while taking Mylan-Candesartan HCTZ, stop the medication and contact your doctor, nurse or pharmacist as soon as possible.

Before you use Mylan-Candesartan HCTZ talk to your doctor, nurse or pharmacist if you:

- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- Have a liver disorder.
- Have a kidney disorder.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with Mylan-Candesartan HCTZ is not recommended.
- Are taking an angiotensin converting enzyme inhibitor (ACEI). You can recognize ACEIs because their medicinal ingredient ends in '-PRIL'.
- Have narrowing of an artery or a heart valve.
- Have heart failure.
- Have diabetes, liver, heart or kidney disease.
- Have lupus.
- Are on dialysis.

- Are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill") or other drugs that may increase potassium levels (e.g., heparin, co-trimoxazole).
- Are on a low-salt diet.
- Are less than 18 years old.
- Are having any kind of surgery or dental procedure with anesthesia.
- Have had a heart attack or stroke.

Hydrochlorothiazide in Mylan-Candesartan HCTZ can cause Sudden Eye Disorders:

- **Myopia**: sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting Mylan-Candesartan HCTZ.

You may become sensitive to the sun while taking Mylan-Candesartan HCTZ. Exposure to sunlight should be minimized until you know how you respond.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to Mylan-Candesartan HCTZ. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or nurse or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Mylan-Candesartan HCTZ:

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amantadine.
- Amphotericin B, an antifungal drug.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Other blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotensin converting enzyme inhibitors (ACEIs). When taken in combination with Mylan-Candesartan HCTZ, they may cause excessively low blood pressure.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, biperiden, domperidone and metoclopramide.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen and celecoxib.
- Pressor amines such as norepinephrine.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurarine.

PROPER USE OF THIS MEDICATION

Take Mylan-Candesartan HCTZ exactly as prescribed. It is recommended to take your dose at about the same time everyday.

Mylan-Candesartan HCTZ can be taken with or without food but it should be taken the same way each day.
Swallow Mylan-Candesartan HCTZ with a glass of water.

If Mylan-Candesartan HCTZ causes upset stomach, take it with food or milk.

To help you keep track of your doses, Mylan-Candesartan HCTZ comes in a Compliance Pack with days of the week printed on the back of the blister. Start with the tablet that matches the day of the week and continue taking them in order until they are all finished.

There are 14 days of labeled tablets in each blister, with one extra to make 15. All 15 tablets, including the one labeled "Take this tablet last", are exactly the same. Once you have finished the 14 labeled tablets take the one marked "Take this tablet last" before starting your next blister pack.

The package protects each tablet. When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.

Do not transfer Mylan-Candesartan HCTZ to other pill containers. To protect your Mylan-Candesartan HCTZ tablets, keep them in the original package.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

Usual Adult Dose:
Usual maintenance dose is: 1 tablet daily

The dosage of Mylan-Candesartan HCTZ is individualized.

Mylan-Candesartan HCTZ is not for initial therapy. You must first be stabilized on the individual components (candesartan cilexetil and hydrochlorothiazide) of Mylan-Candesartan HCTZ.

Overdose:

If you think you have taken too much Mylan-Candesartan HCTZ, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of Mylan-Candesartan HCTZ and remember within 12 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. But if it is more than 12 hours when you remember, do not take the missed dose. Just take the next dose on time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- back or leg pain, muscle cramps, spasms and pain, weakness, restlessness
- dizziness, pins and needles in your fingers, headache
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth
- bleeding under skin, rash, red patches on the skin, itching
- drowsiness, insomnia
- reduced libido
- throat infections
- cough

If any of these affects you severely, tell your doctor, nurse or pharmacist.

Mylan-Candesartan HCTZ can cause abnormal blood test results. 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 to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up	√		
	Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		√	
	Tachycardia: increased heart beats		√	
	Edema: swelling of hands, ankles or feet		√	
Uncommon	**Allergic reactions:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Increased blood sugar: frequent, urination, thirst, and hunger	√		
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Rare	**Rhabdomyolysis:** muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		√	

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains and flu-like symptoms		√	
	Decreased Platelets: bruising, bleeding, fatigue and weakness		√	
Very Rare	**Toxic Epidermal Necrolysis:** severe skin peeling, especially in the mouth and eyes			√
Unknown	**Eye disorders:** **-Myopia:** sudden near sightedness or blurred vision **-Glaucoma:** increased pressure in your eyes, eye pain			√
	Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	
	Lupus: Conditions may be activated or made worse		√	

This is not a complete list of side effects. For any unexpected effects while taking Mylan-Candesartan HCTZ, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- Although the Mylan-Candesartan HCTZ tablets are protected in their package, it is best to keep the package at normal room temperature (15°C to 30°C) and in a dry place. Do not keep Mylan-Candesartan HCTZ in the bathroom.
- **Keep out of sight and reach of children**. Never take medicine in front of small children as they will want to copy you.
- Do not keep or use Mylan-Candesartan HCTZ after the expiry date indicated on the package. Unused medicines, which you know you will no longer need, should be carefully discarded. You may wish to seek advice from your pharmacist.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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

MORE INFORMATION

The document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC, at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC
Etobicoke, Ontario M8Z 2S6

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Mylan

Mylan Pharmaceuticals ULC
Etobicoke, ON M8Z 2S6
1-800-575-1379
www.mylan.ca