Journal of Applied Pharmaceutical Science

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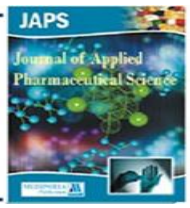

ISSN: 2231-3354
Received on: 25-11-2011
Revised on: 02:12:2011
Accepted on: 19-12-2011

A Review on Candesartan: Pharmacological and Pharmaceutical Profile

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ABSTRACT

Candesartan is classified as an angiotensin II receptor type 1 antagonist. Angiotensin II receptor type 1 antagonists are widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Candesartan is an orally active lipophilic drug and possesses rapid oral absorption. It causes reduction in blood pressure and is used in treatment of hypertension. It is also used in the treatment of congestive heart failure and given as prophylaxis to reduce the severity and duration of migraine. Candesartan cilexetil, a prodrug of Candesartan, is available in the market under the trade names- Blopress®, Atacand®, Amias® and Ratacand®. Candesartan is also available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive effect. This paper reviews the pharmacological and pharmaceutical properties of Candesartan. Candesartan could be an attractive target for the generic industries.

Keywords: Candesartan, Cilexetil, ACE inhibitors, hypertension, diabetes.

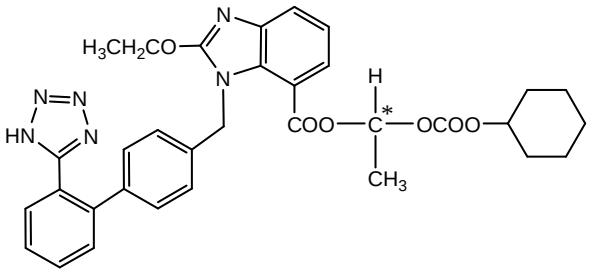
INTRODUCTION

Candesartan is an angiotensin II receptor blocker (ARB). ARBs are widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Candesartan is an orally active non-peptide tetrazole derivative. It finds most significant clinical use in the treatment of hypertension of all grades. Candesartan is a potent, highly selective ARB that is devoid of agonist activity (Belz *et al.*, 1997, Kenakin *et al.*, 1997, Gavras *et al.*, 1993., Zuschke *et al.*, 1999). Candesartan cilexetil is an ester prodrug of its active metabolite Candesartan, to which it owns its therapeutic effect (Gleiter *et al.*, 2004). It is also used in the treatment of congestive heart failure (Pfeffer *et al.*, 2003). Candesartan is used experimentally in preventive treatment of migraine (Tronvik *et al.*, 2003). Hypertension is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult population. Furthermore, hypertension is an independent risk factor for cardiovascular disease and is associated with an increased incidence of stroke and coronary heart disease. Although there have been many advances in the treatment over the past several decades, less than 25% of all hypertensive patients have their blood pressure adequately controlled with available therapies. The angiotensin II angiotensin blockers (ARBs) represent a newer class of antihypertensive agents (Siddiqui *et al*. 2011). Candesartan is indicated in the treatment of hypertension and congestive heart failure (Israili *et al*., 2000., Meredith *et al*., 2007., Ostergren *et al*., 2004, Ross *et al*., 2004., Rossi *et al*., 2006). Candesartan cilexetil is marketed by AstraZeneca and Takeda Pharmaceuticals, commonly under the trade names of Blopress®, Atacand®, Amias® and Ratacand®. Candesartan is also available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive

effect. Candesartan/hydrochlorothiazide combination preparations are marketed under various trade names including Atacand HCT®, Hytacand®, Biopress Plus®, Advantec® and RAtacand Plus® (Merck index, 2006).

PHYSICOCHEMICAL PROPERTIES

Candesartan is a tetrazole derivative (five-membered heterocyclic ring with 4 nitrogen atoms). Clinically it is used in the form of an ester prodrug- Candesartan cilexetil. Candesartan cilexetil is chemically 2-ethoxy-3-[21-(1*H*-tetrazol-5-yl)biphenyl-4 ylmethyl]-3*H*-benzoimiadazole-4-carboxylic acid 1-cyclo-hexyloxycarbonyloxy ethyl ester (**Structure 1**), with chemical formula $C_{33}H_{34}N_6O_6$ and molecular weight 610.67. It is white to off-white powder with melting point 157-160° C. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxy-carbonyloxy- ethyl ester group (Etinger *et al.*, 2006). The solubility in benzyl alcohol is 0.3 M, and the solubility in water is $< 8\times10^{-8}$ M. The partition coefficient ($C_{octanol}/C_{aqueous}$) at pH 1.1, 6.9 & 8.9 is >1000 indicating high hydrophobicity character. It has a pKa value of 6.0 (Cagigal *et al.*, 2001).



Structure 1: Candesartan cilexetil (chiral center is marked by *).

PHARMACOLOGY

Mechanism of Action

The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also affect the renin-angiotensin system. The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect; ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins, and thus, inhibition of ACE may result in accumulation of these substrates; production of angiotensin II can occur through non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE inhibitor effects on the enzyme; and ARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site (Burnier *et al.*, 2000). All 7 drugs (sartans`) in this class are approved by the FDA for the treatment of hypertension, either alone or in combination with other drugs. Unlabeled uses include the treatment of congestive heart failure and, for losartan and irbesartan, diabetic nephropathy (Sankyo Pharma Inc *Benicar(®) product monograph.*, 2002, Olin, 2002). Candesartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water is reabsorbed. The end result is an elevation in blood pressure. Candesartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II. Candesartan cilexetil antagonizes the action of angiotensin II by blocking the angiotensin type-1 (AT1) receptor. Angiotensin II is the primary vasoactive hormone of the renin angiotensin-aldosterone system 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 AT1 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 AT2 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 AT1 receptor than for the AT2 receptor. The strong bond between Candesartan and the AT1 receptor is a result of tight binding to and slow dissociation from the receptor. Candesartan does not inhibit angiotensin converting enzyme (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 (Delacretaz *et al.*, 1995).

Hypertension

Studies with Candesartan cilexetil in healthy volunteers and patients with hypertension have shown a significant and long lasting decrease of systolic and diastolic blood pressure (Ogihara *et al.*, 1994., Ogihara *et al.*, 1993., Hubner *et al.*, 1997, Sever *et al.*, 1997). In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function, including serum levels of total cholesterol, triglycerides, glucose, or uric acid. Same observations were observed in a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension (ATACAND® product monograph)

Heart Failure

In heart failure patients, Candesartan ≥8 mg resulted in decreased systemic vascular resistance and pulmonary capillary wedge pressure (Olin, 2002).

PHARMACOKINETIC & PHARMCODYNAMIC PROFILE

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the

gastrointestinal tract to Candesartan, a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by *o*-de-ethylation to an inactive metabolite. The elimination half-life of Candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of Candesartan is linear for oral doses up to 32 mg of Candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing (Meineke *et al.*, 1997).

Candesartan is poorly absorbed after oral administration, therefore the ester prodrug Candesartan cilexetil was prepared (Imamiya, *et al.*, 1993, Kubo, *et al.*.1993). This prodrug is rapidly and completely converted to the active compound Candesartan during gastrointestinal absorption (Morimoto *et al.*, 1994, Kondo *et al*., 1996). In healthy subjects 67% of an oral dose of Candesartan is excreted in faeces (Van Lier *et al*., 1997) and only about 5% to 10% of the administered dose is excreted unchanged in the urine in 24 h (Ogihara *et al*., 1994., Riddell *et al*., 1997).

Despite compensatory increase in plasma renin activity and plasma angiotensin II levels, the relationship between the time-integrated systolic blood pressure response to angiotensin II and the time-integrated levels of Candesartan is consistent (Delacretaz *et al*., 1995). Pharmacokinetic parameters of Candesartan and other ARB are given in (**Table 1**).

Table 1: Comparison of ARB Pharmacokinetics.

Drug	Trade Name	Biological half life [in hour]	Protein binding [%]	Bioavailability [%]	Renal/hepatic clearance [%]	Food effect	Daily dosage [mg]
Losartan	Cozaar	2	98.7	33	10/90	Minimal	50–100
EXP 3174		6–9	99.8	–	50/50	–	–
Candesartan	Atacand	9	>99	15	60/40	No	4–32
Valsartan	Diovan	6	95	25	30/70	No	80–320
Irbesartan	Avapro	11–15	90–95	70	1/99	No	150–300
Telmisartan	Micardis	24	>99	42–58	1/99	No	40–80
Eprosartan	Teveten	5	98	13	30/70	No	400–800
Olmesartan	Benicar	14–16	>99	29	40/60	No	10–40
Azilsartan	Edarbi	11	>99	60	55/42	No	40–80

Absorption

Administration of the Candesartan cilexetil prodrug, the absolute bioavailability of Candesartan was estimated to be 15%. Food with a high fat content has no affect on the bioavailability of Candesartan from Candesartan cilexetil (Ross *et al*., 2004).

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 crosses the blood-brain barrier poorly. It has also been demonstrated in rats that Candesartan passes across the placental barrier and is distributed in the fetus (Meineke *et al*., 1997).

Metabolism and Excretion

Total plasma clearance of Candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When Candesartan is administered orally, about 26% of the dose is excreted unchanged 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 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 (Meineke *et al.*, 1997, Van Lier *et al.*, 1997).

Pharmacodynamics

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of Candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 h. Plasma concentrations of angiotensin I and 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. ACE activity was not altered in healthy subjects after repeated Candesartan cilexetil administration. The once-daily administration of up to 16 mg of Candesartan Cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of Candesartan cilexetil was administered to hypertensive patients (Buter *et al.*, 1999., Azizi *et al.*, 1999).

THERAPEUTIC EFFICACY

The therapeutic efficacy of Candesartan has been evaluated in a number of dose ranging and comparative studies in patients with varying degrees of hypertension, and heart failure.

Hypertension

The antihypertensive effects of Candesartan cilexetil (Atacand) were examined in 14 placebo-controlled trials of 4- to 12-weeks duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 95 to 114 mm Hg. Most of the trials were of Candesartan cilexetil as a single agent, but it was also studied as add-on to hydrochlorothiazide and amlodipine. These studies included a total of 2350 patients randomized to one of several doses of Candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2 to 32 mg on trough (24 h) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg. There were no exaggerated first-dose effects in these patients. Most of the antihypertensive effect was seen within 2 weeks of initial dosing and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effects of Candesartan cilexetil and losartan potassium at their highest recommended doses administered once-daily were compared in two randomized, double-blind trials. In a total of 1268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, Candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect. The antihypertensive effects of twice daily dosing of either Candesartan cilexetil or losartan potassium were not studied.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to 1 year, the antihypertensive effectiveness of Candesartan cilexetil was maintained, and there was no rebound after abrupt withdrawal. There were no changes in the heart rate of patients treated with the drug in controlled trials (ATACAND® product monograph, Ogihara *et al.*, 1994., Ogihara *et al.*, 1993., Hubner *et al.*, 1997, Sever *et al.*, 1997).

Heart Failure

Candesartan was studied in two heart failure outcome studies:

1. The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity trial in patients intolerant of ACE inhibitors (CHARM−Alternative).

2. CHARM−Added in patients already receiving ACE inhibitors. Both studies were international double-blind, placebo-controlled trials in patients with NYHA class II - IV heart failure and LVEF ≤ 40%. In both trials, patients were randomized to placebo or Atacand (initially 4-8 mg once daily, titrated as tolerated to 32 mg once daily) and followed for up to 4 years. Patients with serum creatinine ≥3 mg/dL, serum potassium ≥ 5.5 mEq/L, symptomatic hypotension or known bilateral renal artery stenosis were excluded. The primary end point in both trials was time to either cardiovascular death or hospitalization for heart failure (ATACAND® product monograph).

Renal Insufficiency

In hypertensive patients with renal insufficiency, serum concentrations of Candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m2) compared to patients with normal kidney function. The pharmacokinetics of Candesartan in hypertensive patients undergoing hemodialysis is similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency.

In heart failure patients with renal impairment, $AUC_{0\text{-}72h}$ was 36% and 65% higher in mild and moderate renal impairment, respectively. C_{max} was 15% and 55% higher in mild and moderate renal impairment, respectively. (ATACAND® product monograph).

Hepatic Insufficiency

The pharmacokinetics of Candesartan was compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg Candesartan cilexetil. The increase in AUC for Candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in C_{max} for Candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after Candesartan cilexetil administration has not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In hypertensive patients with moderate hepatic impairment, consideration should be given to initiation of the drug at a lower dose. (ATACAND® product monograph).

Heart Failure

The pharmacokinetics of Candesartan was linear in patients with heart failure (NYHA class II and III) after Candesartan cilexetil doses of 4, 8, and 16 mg. After repeated dosing, the AUC was approximately doubled in these patients compared with healthy, younger patients. The pharmacokinetics in heart failure patients is similar to that in healthy elderly volunteers (ATACAND® product monograph).

USES

Candesartan cilexetil is widely used for the treatment of hypertension and heart failure in clinical application (Israili *et al.*, 2000, Meredith *et al.*, 2007, Ostergren *et al.*, 2004). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. This drug works by relaxing blood vessels so blood can flow more easily. Candesartan belongs to a class of drugs called angiotensin receptor blockers. This medication is also used to treat congestive heart failure. This section contains uses of this drug that are not listed in the approved professional labelling for the drug but that may be prescribed by your health care professional. Use this drug for a condition that is listed in this section only if it has been so prescribed by your health care professional. This drug may also be used to help protect the kidneys from damage due to diabetes (Bell *et al.*, 1999).

DOSAGE AND TOLERABILITY

Dosage

The recommended starting dosage of Candesartan for most adults with high blood pressure (hypertension) is Candesartan 16 mg once a day. Based on the blood pressure response or Candesartan side effects, the dosage may be increased or decreased. With each change in dosage, it may take several weeks to see the full effects of Candesartan on lowering blood pressure.

Most people require a final dose of Candesartan 2 mg to 32 mg either as one daily dose or two smaller doses. It is available in 4 mg, 8 mg, 16 mg, and 32 mg (ATACAND® product monograph).

Overdosage

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of Candesartan cilexetil. In mice given single oral doses of the primary metabolite, Candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The most likely manifestation of overdosage with Candesartan cilexetil would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Candesartan cannot be removed by hemodialysis.

Adverse effects

Common adverse effects are as follows:

- CNS: Headache, dizziness, syncope, muscle weakness
- Cardiovascular : Hypotension
- Dermatologic: Rash, inflammation, urticaria, pruritus, alopecia, dry skin
- Gastro-intestinal: Diarrhea, abdominal pain, nausea, constipation, dry mouth, dental pain
- Respiratory: URI symptoms, cough, sinus disorders
- Other: Cancer in preclinical studies, back pain, fever, gout.

Precautions

When used in pregnancy, angiotensin receptor (AT1) blockers (ARBs) can cause injury or even death of the developing foetus. When pregnancy is detected, Candesartan should be discontinued as soon as possible.

DRUG INTERACTIONS

Candesartan can potentially interact with a number of other medications. Some of these Candesartan interactions include:

Diuretics

- When using Candesartan with a diuretic, the blood pressure may decrease too much. This is more likely to occur when Candesartan is first started. In order to decrease the chances of this interaction, healthcare provider may change the dosages of either medicine, start with on a lower dose of Candesartan, and monitor the more closely. Diuretics like torsemide, furosemide & hydrochlorothiazide interact with Candesartan. Potassium-sparing diuretics, such as spironolactone, triamterene & amiloride, have also shown interactions.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Candesartan can interact with NSAIDs in several ways. The combination could cause blood pressure to increase or may cause swelling (edema), especially in patients with congestive heart failure (CHF). If elderly, have kidney disease or kidney failure, or are taking a diuretic ("water pill") or are dehydrated, taking NSAIDs and Candesartan together may cause kidney failure. NSAIDs such as Celecoxib, Diclofenac, Ibuprofen, Indomethacin, Ketoprofen, Naproxen cause interactions with Candesartan.

Potassium Supplements

If using a potassium supplement with Candesartan, the levels of potassium in the blood may become too high. This can cause serious problems.

Lithium

Using a lithium preparation with Candesartan can pose a serious problem due to interaction.

CONCLUSION

Candesartan is a potent, long-acting, non-peptide tetrazole derivative, angiotensin II receptor antagonist having high selectivity for the AT1 subtype (angiotensin I). Candesartan reduces the blood pressure and is an effective antihypertensive agent in patients with mild to moderate hypertension. The drug also reduces blood pressure when used as monotherapy in patients with severe hypertension or when used adjunctively in patients with resistant hypertension. Importantly, Candesartan is safer, more tolerable and as effective as other commonly used antihypertensive agents. The drug therefore represents a useful therapeutic option in the management of patients with hypertension and congestive heart failure will be particularly useful in patients not responding to, or intolerant of, anti-hypertensive agents from other drug classes. It could be an attractive target for the generic industries.

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