Atasart™

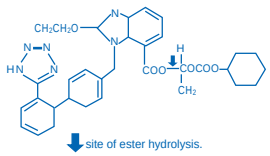
[Candesartan Cilexetil Tablets]

8mg & 16mg Tablets

DESCRIPTION

ATASART (Candesartan Cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Candesartan Cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Its molecular formula is $C_{33}H_{34}N_6O_6$ and the structural formula is:



site of ester hydrolysis.

(Candesartan Cilexetil)

QUANTITATIVE & QUALITATIVE COMPOSITION

ATASART (Candesartan Cilexetil) is available for oral administration as:

1. ATASART Tablets 8mg
   Each tablet contains:
   Candesartan Cilexetil ……. 8mg

2. ATASART Tablets 16mg
   Each tablet contains:
   Candesartan Cilexetil ……. 16mg

CLINICAL PHARMACOLOGY

Mechanism of Action

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 is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Pharmacokinetics

Absorption:

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.

Following administration of Candesartan Cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after Candesartan Cilexetil administration.

Metabolism:

Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite.

Distribution:

After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32mg of Candesartan Cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

The volume of distribution of candesartan is 0.13L/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.

Excretion:

When candesartan is administered orally about 26% of the dose is excreted unchanged in urine. Total plasma clearance of candesartan is 0.37mL/min/kg, with a renal clearance of 0.19mL/min/kg. The elimination half-life of candesartan is approximately 9 hours.

Special Populations

Pediatric

The pharmacokinetics of Candesartan Cilexetil have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of candesartan have been studied in the elderly (>65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered with 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. No initial dosage adjustment is necessary.

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 <30mL/min/1.73m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are 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 mild renal insufficiency.

Hepatic Insufficiency

The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16mg 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 have not been investigated in patients with severe hepatic impairment.

THERAPEUTIC INDICATIONS

ATASART (Candesartan Cilexetil) is indicated for the treatment of:

- Essential hypertension in adults
- Hypertension in children and adolescents aged 6 to <18 years.
- Hypertension with intravascular volume depletion
- Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) when Angiotensin Converting Enzyme (ACE) inhibitors are not tolerated or as add-on therapy to ACE inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated.

DOSAGE AND ADMINISTRATION

Hypertension:

The recommended initial dose and usual maintenance dose is 8mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.

Atasart (Candesartan Cilexetil) Tablets may also be administered with other antihypertensive agents. Addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses Atasart (Candesartan Cilexetil) Tablets.

Hypertension with intravascular volume depletion:

Adult: Initially 4mg once daily, increased if necessary up to 32mg daily, doses to be increased at intervals of 4 weeks; usual dose 8mg once daily.

Elderly people:

No initial dose adjustment is necessary in elderly patients.

Patients with intravascular volume depletion:

An initial dose of 4mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion.

Patients with renal impairment:

The starting dose is 4 mg in patients with renal impairment, including patients on hemodialysis. The dose should be titrated according to response. There is limited experience in patients with very severe or end-stage renal impairment (Cl creatinine < 15 ml/min)

Patients with hepatic impairment:

An initial dose of 4mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to response. Atasart is contraindicated in patients with severe hepatic impairment and/or cholestasis

Black patients:

The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. Consequently, up titration of Atasart (Candesartan Cilexetil) Tablets and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients.

Pediatric Population:

Children and adolescents aged 6 to <18 years:

The recommended starting dose is 4 mg once daily.

- For patients weighing < 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 8 mg once daily.
- For patients weighing ≥ 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to 8 mg once daily and then to 16 mg once daily if needed.

Doses above 32 mg have not been studied in pediatric patients.

Most of the antihypertensive effect is attained within 4 weeks.

For children with possible intravascular volume depletion (e.g., patients treated with diuretics, particularly those with impaired renal function), Atasart treatment should be initiated under close medical supervision and a lower starting dose than the general starting dose above should be considered.

Atasart has not been studied in children with glomerular filtration rate less than 30 ml/min/1.73m^2.

Black Paediatric patients:

The antihypertensive effect of Atasart (Candesartan Cilexetil) is less pronounced in black patients than in non-black patients.

Children aged below 1 year to <6 years

The safety and efficacy in children aged 1 to <6 years of age has not been established.

Atasart (Candesartan Cilexetil) is contraindicated in children aged below 1 year.

Heart Failure

The usual recommended initial dose of Atasart (Candesartan Cilexetil) Tablets is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks

Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium. Atasart can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products. Atasart may be co-administered with an ACE-inhibitor in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor antagonists are not tolerated. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Atasart is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

Special patient populations

No initial dose adjustment is necessary for elderly patients or in patients with intravascular volume depletion or renal impairment or mild to moderate hepatic impairment.

Pediatric Population
The safety and efficacy of Atasart in children aged between birth and 18 years have not been established in the treatment of heart failure. No data are available.

Method of administration:
Oral use. Should be taken once daily with or without food.

ADVERSE REACTIONS
In general, treatment with Candesartan Cilexetil was well tolerated. however the following adverse reactions have been reported;
Common: Respiratory infection, Dizziness/vertigo, headache,
Rare: Leukopenia, neutropenia and agranulocytosis, Hyperkalaemia, hyponatremia, Cough, Nausea, Increased liver enzymes, abnormal hepatic function or hepatitis, Angioedema, rash, urticaria, pruritus, Back pain, arthralgia, myalgia, Renal impairment, including renal failure in susceptible patients.
Not known: Diarrhea

Pediatric Population
Common: Headache, Dizziness, Upper respiratory tract infection, Cough, Rash, Sinus arrhythmia, Nasopharyngitis, pyrexia and oropharyngeal pain.

Uncommon: Hyperkalemia, hyponatremia and abnormal liver function.
The overall safety profile for candesartan Cilexetil in Paediatric patients does not differ significantly from the safety profile in adults.

CONTRAINDICATIONS
- Hypersensitivity to Candesartan Cilexetil or to any of the excipient of product.
- Severe hepatic impairment and/or cholestasis.
- The concomitant use of Candesartan Cilexetil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2)
- Second and third trimesters of pregnancy.
- Children aged below 1 year

WARNINGS / PRECAUTIONS

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, candesartan cilexetil should be discontinued as soon as possible.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
Concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkaliemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
Renal impairment:
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with Candesartan Cilexetil.
When Candesartan Cilexetil is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment (Cl creatinine < 15 ml/min). In these patients Candesartan Cilexetil should be carefully titrated with thorough monitoring of blood pressure.
Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan Cilexetil, monitoring of serum creatinine and potassium is recommended.
Hemodialysis:
During dialysis the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, Candesartan Cilexetil should be carefully titrated with thorough monitoring of blood pressure in patients on hemodialysis.
Concomitant therapy with an ACE inhibitor in heart failure:
The risk of adverse reactions, especially hypotension, hyperkaliemia and decreased renal function (including acute renal failure), may increase when used in combination with an ACE inhibitor. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and Candesartan Cilexetil is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. Use of ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
Hypotension:
Hypotension may occur during treatment with Candesartan Cilexetil in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.
For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), candesartan treatment should be initiated under close medical supervision and a lower starting dose should be considered.
Anesthesia and surgery:
Hypotension may occur during anesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.
Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy):
As with other vasodilators, special caution is indicated in patients suffering from hemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.
Primary hyperaldosteronism:
Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use is not recommended in this population.
Hyperkalaemia:
Concomitant use of Candesartan Cilexetil with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients. Monitoring of potassium should be undertaken as appropriate.
In heart failure patients treated with Candesartan Cilexetil, hyperkaliemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan Cilexetil is not recommended and should be considered only after careful evaluation of the potential benefits and risks.
General:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with AIIRAs. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.
The antihypertensive effect of candesartan may be enhanced by other medicinal products with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.
Atasart (Candesartan Cilexetil) Tablets 8mg & 16mg contains lactose. Patients with rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Hypotension in Volume- and Salt-Depleted Patients:
In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of Candesartan Cilexetil, or the treatment should start under close medical supervision. If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.
Impaired Renal Function:
Renal artery stenosis: Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor antagonists (AIIRAs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Pregnancy
The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.

Nursing Mothers
It is not known whether candesartan is excreted in human milk but because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions
- Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.
- No significant drug interactions have been reported in studies of Candesartan Cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers.
- Since both, ACE inhibitors and angiotensin receptor blockers, can increase the concentrations of potassium in the blood, other medications that can increase the concentration of potassium in the blood, such as *spironolactone*, and *potassium supplements*, should be used cautiously with candesartan.
- Reversible increases in serum *lithium* concentrations and toxicity have been reported during concomitant administration of *lithium* with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum *lithium* concentration has been reported during concomitant administration of *lithium* with Candesartan Cilexetil, so careful monitoring of serum *lithium* levels is recommended during concomitant use.
- When AIIRAs are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
- As with ACE inhibitors, concomitant use of AIIRAs 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 preexisting renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Effects on ability to drive and use machines
No studies on the effects of candesartan on the ability to drive and use machines have been performed. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with Atasart (Candesartan Cilexetil). Therefore, it may impair the patient's ability to concentrate and react and may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Overdosage
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.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
ATASART (Candesartan Cilexetil) 8mg tablets are available in alu-alu blister packs of 28's.
ATASART (Candesartan Cilexetil) 16mg tablets are available in alu-alu blister packs of 28's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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