4. DRUG PROFILE

Name: Candesartan Cilexetil

4.1 Introduction:

Candesartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. The prodrug candesartan cilexetil is marketed by Astrazeneca and takeda Pharmaceuticals, commonly under the trade names Blopress, Atacand, Amias and Ratacand. [53, 54]

4.2 Physicochemical properties: [54,55]

- **Pharmacopoeial specification:** Official in European Pharmacopoeia 2012 and USP-NF 35-30
- **Description:** White or almost white crystalline powder.
- **Structure:**

![Chemical Structure of Candesartan Cilexetil]

- **Chemical name:** 2-ethoxy-1-\{(4-[2-(2H-1,2,3,4-tetrazol-5yl) phenyl] phenyl} methyl\) - 1H-1, 3-benzodiazole-7-carboxylic acid
- **Molecular formula:** C_{24}H_{20}N_{6}O_{3}
- **State:** Solid
- **Molecular weight:** 440.45g/mol
- **Solubility:**
  - Insoluble in water (7.71e-03 g/l)
  - Soluble in methanol
- **pKa:** 7.4
- **log P:** 4.0
4.3 Mechanism of Action: [56]

Candesartan selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Candesartan is greater than 10,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion.

4.4 Pharmacodynamics: [56]

Candesartan cilexetil is an ARB prodrug that is rapidly converted to candesartan, its active metabolite, during absorption from the gastrointestinal tract. Candesartan confers blood pressure lowering effects by antagonizing the hypertensive effects of angiotensin II via the RAAS. RAAS is a homeostatic mechanism for regulating hemodynamics, water and electrolyte balance. During sympathetic stimulation or when renal blood pressure or blood flow is reduced, renin is released from granular cells of the juxtaglomerular apparatus in the kidneys. Renin cleaves circulating angiotensinogen to angiotensin I, which is cleaved by angiotensin converting enzyme (ACE) to Angiotensin II. Angiotensin II increases blood pressure by increasing total peripheral resistance, increasing sodium and water reabsorption in the kidneys via aldosterone secretion, and altering cardiovascular structure. Angiotensin II binds to two receptors: type-1 angiotensin II receptor (AT1) and type-2 angiotensin II receptor (AT2). AT1 is a G-protein coupled receptor (GPCR) that mediates the vasoconstrictive and aldosterone-secreting effects of angiotensin II. Studies performed in recent years suggest that AT2 antagonizes AT1-mediated effects and directly affects long-term blood pressure control by inducing vasorelaxation and increasing urinary sodium excretion. Angiotensin receptor blockers (ARBs) are non-peptide competitive inhibitors of AT1. ARBs block the ability of angiotensin II to stimulate pressor and cell proliferative effects. Unlike ACE inhibitors, ARBs do not affect bradykinin-induced vasodilation. The overall effect of ARBs is a decrease in blood pressure.
4.5 Pharmacokinetics: [56]

➢ Absorption:
Following 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.

➢ Metabolism: [56]
The prodrug candesartan cilexetil undergoes rapid and complete ester hydrolysis in the intestinal wall to form the active drug, candesartan. Elimination of candesartan is primarily as unchanged drug in the urine and, by the biliary route, in the feces. Minor hepatic metabolism of candesartan (<20%) occurs by O-deethylation via cytochrome P450 2C9 to form an inactive metabolite. Candesartan undergoes N-glucuronidation in the tetrazole ring by uridine diphosphate glucuronosyltransferase 1A3 (UGT1A3). O-glucuronidation may also occur. 75% of candesartan is excreted as unchanged drug in urine and feces.

➢ Route of elimination: [56]
When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Candesartan is mainly excreted unchanged in urine and feces (via bile).

➢ Half life: Approximately 9 hours.
➢ Clearance: 0.37 mL/min/kg

4.6 Indications: [56]
Indications for its use include:

➢ May be used as a first line agent to treat uncomplicated hypertension, isolated systolic hypertension and left ventricular hypertrophy.
➢ May be used as a first line agent to delay progression of diabetic nephropathy.
➢ Candesartan may be also used as a second line agent in the treatment of congestive heart failure, systolic dysfunction, myocardial infarction and coronary artery disease in those intolerant of ACE inhibitors.
4.7 Cautions: [56]

- Pregnancy
- If renal artery stenosis or impairment
- If hepatic impairment
- If volume depletion
- If hyponatremia

4.8 Side-effects: [56]

- Back pain
- Dizziness
- Upper respiratory tract infection
- Pharyngitis
- Rhinitis

4.9 Dose: [56]

- 2 to 32 mg per day.
- The dosage is based on the desired antihypertensive effect and on how the individual patient tolerates the medicine.
- **Recommended initial dose:** Usual recommended starting dose is 16 mg once daily when used as monotherapy.
- **Maximum permitted daily dose:** 32 mg.
- It can be administered once or twice daily with total daily doses ranging from 8 to 32 mg.
4.10 Interactions for Candesartan Cilexetil:

Not substantially metabolized by CYP isoenzymes; has no effect on CYP isoenzymes at therapeutic concentrations. [57]

Table 4.7: Interactions for Candesartan Cilexetil

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac drugs (e.g., digoxin, enalapril, hydrochlorothiazide, nifedipine)</td>
<td>Pharmacologic interactions unlikely[^57,58,59]</td>
<td>-</td>
</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Pharmacokinetic interaction unlikely[^57,58,59]</td>
<td>-</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Pharmacologic interaction unlikely[^57,58]</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>Increased serum lithium concentrations; possible toxicity[^57]</td>
<td>Closely monitor serum lithium concentrations</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Pharmacologic interaction unlikely[^57,58,59]</td>
<td>-</td>
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</tbody>
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