Drug Profile of Telmisartan
4. DRUG PROFILE OF TELMISARTAN

Telmisartan is in the drug class of angiotensin receptor blockers (ARBs) and is prescribed for the treatment of high blood pressure, reducing the risk of heart attack, stroke, or death from cardiovascular causes.

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.

4.1. Structure

Fig:6. Structure of Telmisartan.
Chemical Name:-
[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl] 1,1 ' biphenyl] – 2 carboxylic acid.

Molecular Formula:- C$_{33}$H$_{30}$N$_{4}$O$_{2}$

Molecular Weight:- 514.61

Description:- White to off-white crystalline powder.

Melting range:- Between 265.0°C and 272.0°C

Solubility:- Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride, it dissolves in 1M sodium hydroxide.

Partial coefficient:- The Octanol/buffer partial coefficient (log P) for Telmisartan is approximately 3.20

Storage & Stability:- Stored in well-closed, light-resistant containers at 5-30°C. When stored under these conditions, Telmisartan generally is stable for 24 months after the date of manufacture.

Indication:- For the treatment of hypertension

4.2. Clinical Pharmacology:-

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT$_1$ receptor subtype. New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

Mechanism of Action:-

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT$_1$-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels.
4.3. Pharmacokinetic properties;
Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC_{0-∞}) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution
Telmisartan is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).
4.5. PHARMACOKINETICS

Absorption

Absolute bioavailability depends on dosage. Food slightly decreases the bioavailability (a decrease of about 6% is seen when the 40-mg dose is administered with food).

Toxicity

Intravenous LD$_{50}$ in rats is 150-200 mg/kg in males and 200 to 250 mg/kg in females. Acute oral toxicity is low: no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest dose tested. Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Protein Binding

Highly bound to plasma proteins (>99.5%), mainly albumin and α1-acid glycoprotein. Binding is not dose-dependent.

Biotransformation

Minimally metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.
Dosage and Administration:

The usually effective dose telmisartan is 40–80 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily.

Contraindications

Telmisartan is contraindicated during pregnancy. Like other drugs affecting the renin angiotensin system (RAS), telmisartan can cause birth defects, stillbirths, and neonatal deaths. It should not be taken by breastfeeding women since it is not known whether the drug passes into the breast milk.

Side effects

Side effects are similar to other angiotensin II receptor antagonists and include tachycardia and bradycardia (fast or slow heartbeat), hypotension (low blood pressure), edema (swelling of arms, legs, lips, tongue, or throat, the latter leading to breathing problems), and allergic reactions.

4.5. List of available formulation for Telmisartan

Table: 3.

<table>
<thead>
<tr>
<th>Route</th>
<th>Form</th>
<th>Brand</th>
<th>Company</th>
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<tbody>
<tr>
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<td>Telma tablets</td>
<td>Glenmark</td>
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<td>Zitelmi</td>
<td>FDC Ltd</td>
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<td>Medley pharma</td>
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<td>Tablets</td>
<td>Cesar</td>
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