3.1. RANITIDINE BISMUTH CITRATE

**Chemical Name**: N-[2-(5-Dimethylamino methyl-furan-2-yl methyl sulfanyl)–ethyl]–N–methyl-2-nitro-1,1-ethane diamine bismuth citrate.

**Molecular weight**: 715.50

**Molecular Formula**: C_{13}H_{22}N_{4}O_{3}S. Bi. C_{6}H_{8}O_{7}.

**Category**: Histamine H\textsubscript{2} receptor antagonist with \textit{H. pylori} suppressive activity.

**Description**: A white to off white amorphous powder. 400 mg of ranitidine bismuth citrate is equivalent to ranitidine base 162 mg, trivalent bismuth 128 mg and citrate 110 mg.

**Solubility**: Highly soluble in water 837 g/L and other aqueous solvents and practically insoluble in organic solvents, alcohols, and fixed oils. The solubility of RBC between pH 4.3 and 3.9 is 100 %, although this drops progressively equivalent to 4% bismuth solubility at pH 2.2.

**pH**: 1% w/v solution in water has a pH of 4.6.

**Storage**: It should be kept in tightly closed container away from moisture and source of ignition. Prolonged storage at elevated temperatures should be avoided. It should be stored between 25 to 30°C in a dry place.

**Mode of action**: Ranitidine bismuth citrate is histamine H\textsubscript{2} receptor antagonist with anti \textit{H. pylori} and mucosal protective activity. It is a complex of ranitidine and bismuth citrate which together produce \textit{H. Pylori} suppressive activity. Ranitidine bismuth citrate is bactericidal to \textit{H Pylori in vitro} and has gastric protective action. After oral
administration of ranitidine bismuth citrate, it dissociates in intragastric fluid giving rise to the formation of ranitidine and soluble or insoluble forms of bismuth. It inhibits basal and simulated gastric acid secretion and reduces both the volume and pepsin content of the secretion. It dose not alter plasma pepsinogen I and II concentration or pepsin activity and it has no clinically relevant effect on fasting or postprandial plasma gastrin. The effectiveness of ranitidine bismuth citrate in eradication of *H Pylori in vivo* has been shown to be enhanced by the addition of antibiotics such as clarithromycin and amoxicillin.

**Pharmacokinetics:** Following ingestion ranitidine bismuth citrate dissociates in the intragastric fluid giving rise to ranitidine and soluble or insoluble form of bismuth. Approximately 50% of the ranitidine is absorbed with a peak plasma concentration of 433 ng / ml. About 95% of drug is absorbed with peak plasma concentration of 479 ng /mL within 0.5 to 5 hrs after administration of 400 mg dose. Absorption of ranitidine is not significantly impaired by administration of food. The elimination half life (t1/2) of ranitidine bismuth citrate is 3 hrs after oral dosing and dose not accumulate in the plasma with twice daily dosing. The principal route of elimination of ranitidine is by urinary excretion and accounting for 30 to 40% of the dose. Renal clearance rate of 580 to 680 ml/min is primarily due to active tubular secretion. In renal impaired patients the decreased renal clearance ranging from 120 to 140 ml /min are highly correlated with decline renal function while non renal elimination is unaltered. Elimination half life may exceed 6 hrs in severely impaired renal function i.e. creatinine clearance is less than 25 ml /min. The Volume of distribution of ranitidine is 0.8 to 1.8 L/ kg and serum protein binding capacity is 15%. Oral absorption of bismuth is variable and less than 1% of bismuth derived from ranitidine bismuth citrate is absorbed after oral administration with a peak bismuth concentration of 4.2 ng / mL occurring 15 to 60 min after a 400 mg dose. Absorption of bismuth derived from ranitidine bismuth citrate is also not significantly affected by administration of food or antacids. The absorption of bismuth from ranitidine bismuth citrate is increased when gastric pH exceeds at 6 after dosing and AUC increased from a mean concentration of 16 to 48.3 ng /ml .hr. Bismuth is 98% bound to human plasma protein albumin. In man, bismuth accumulate in plasma during twice daily dose
reaching at least 70% of steady state concentration (less than 20 ng/ml) after 4 week of recommended dose. Elimination of bismuth is poly exponential with a terminal elimination half life of 11 to 28 days. The average renal clearance rate of bismuth is 30 to 60 ml/min indicating nearly equal to tubular reabsorption. Bismuth concentration in renal impaired and elderly patients is increased as a result of decreased renal elimination and also undergoes minor excretion in the bile. Unabsorbed bismuth is excreted through the faces.

**Over dosage:** Adverse effect related overdose with ranitidine are usually reversible, nonspecific, non life threatening and no adverse squeals seen in clinical trials of ranitidine bismuth citrate. Bismuth intoxication from prolonged overdosage or deliberate self poisoning with soluble bismuth compounds can result in neurotoxicity and nephrotoxicity. In the overdose or suspected bismuth toxicity gastric lavage should be employed to remove absorbed material from the GI tract, monitoring the symptoms and other supportive therapy should be employed if indicated. Finally the ranitidine and bismuth components may be removed from the plasma by hemodialysis.

**Table 3.1.1. Adverse drug reactions of ranitidine bismuth citrate reported in controlled trials**

<table>
<thead>
<tr>
<th>Organ /Tissues</th>
<th>Disorders</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Blackening of the stools</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Common</td>
</tr>
<tr>
<td>Mouth</td>
<td>Blackening of tongue</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin</td>
<td>Rashes, pruritis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Allergy Anaphylaxis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood</td>
<td>Anemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Liver function tests</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

* Very Common (> 10%), Common (1-10%), Uncommon (< 1%), Rare (< 0.1%)
Chapter-3

Drug Profile

Contra indications: The ranitidine bismuth citrate contraindicated in patients known to have hyper sensitivity to the drug or its ingredients. Ranitidine bismuth citrate should not be used in patients with a history of porphyria. Administration of is not recommended in patients with severe renal impairment.

Dose: The recommended adult dose for eradicating *H. pylori* is 400 mg twice daily plus antibiotic for 4 weeks. Ranitidine bismuth citrate is not recommended in patients with severe renal impairment (Creatinine clearance less than 25 µg/min).

Marketed Products:
- Trite (UK) Tablet: 400 mg
- Pylorid (Australia) Tablet: 400 mg

Analytical methods of ranitidine bismuth citrate:
- Holnjec et al., (1986) reported a TLC method, in which the purity of ranitidine can be quickly assessed by TLC over silica gel, its R_f value in mobile phase Ethyl acetate: methyl alcohol: diethyl amine (3:3:1) is 0.50 when spot can be located either under an UV lamp or by staining through exposure to iodine vapour.

- Hohnjec et al., (1981a) have developed the HPLC method for the estimation of ranitidine using a HPLC instrument, LC-3-x.p with an UV-LC detector. The chromatograms were run through a column filled with Li-chromosorb RP-8 (5µm) using a mixture of acetonitrile, methanol, water and concentrated ammonia having a pH value of 7.4 as a mobile phase. The elution was carried out under (20,000-25,000 p.s.i.) pressure with a flow rate of 1 cm³/ minand the effluent was monitored optically at 217 nm.

- Hohnjec et al., (1981 b) have developed a spectrophotometric method for the determination of ranitidine. The absorbtion maximum was found to be at 313 nm in water.

- Fellows et al., (1980) have reported a radioimmunoassay method for the determination of ranitidine in plasma. The plasma concentration-time curves after oral administration showed in some cases two peaks and in others a flat plasma concentration profile for upto 3 hours. No such second peak in the plasma concentration curve was seen after intravenous injection.
3.2  Amoxycillin Trihydrate

![Chemical Structure of Amoxycillin Trihydrate]

**Chemical Name**: 6 (R)-6-(α-d- (4-hydroxy phenyl) glycyl amino Penicillionic acid) trihydrate.

**Molecular Weight**: 419.5

**Microbial Source**: *Penicillinium Notatum*

**Molecular Formula**: C_{10}H_{18}N_{3}O_{5}S.3H_{2}O

**Category**: Antibacterial

**Description**: A white or almost white crystalline powder. 1.15g of amoxicillin trihydrate is approximately equivalent to 1g of amoxicillin.

**Solubility**: Slightly soluble in water, methanol and alcohol. Practically insoluble in tetra chloromethane, chloroform, ether, fixed oils. It dissolves in dilute solution of acid and alkali hydroxide.

**pH**: 0.2% solution in water has a pH 3.5 to 6.0.

**Storage**: It should be store at a temperature not exceeding 30°C in airtight container.

**Mechanism of action**: Amoxycillin is known to interfere with the synthesis of peptidoglycans, which are the part of the cell wall material. Several wall enzymes are reversibly inhibited. The most important being a D, D carboxypeptidase which also function as a trans peptidase due to the amino group side chain attached to the basic penicillin structure. Amoxicillin is better able to penetrate the outer membrane of some gram (-) bacteria and has broad spectrum of activity (Tripathi, 2004).

**Pharmacokinetic**: It is more rapidly and more completely absorbed than ampicillin when given by mouth and is reported to produce peak antibiotic plasma concentration
at least twice those from a similar dose of ampicillin. It is resistant to inactivation by the acid of gastric secretion. Peak plasma amoxicillin concentration of about 5μg/ml has been obtained 1 to 2 hrs after a dose of 250 mg, with detectable concentration present for up to 8 hrs. The absorption of amoxicillin is not affected by the food. About 20% is bound to the plasma protein in the circulation with plasma half life of 1 to 1.56 hr. The half life may be longer in neonates and the elderly. In renal failure, half life has been increased and found to be 7 to 20 hrs. It is widely distrusted at vary low concentration in body tissue and fluid. It crosses the placenta. It is metabolized to a limited extent to penicillonic acid, which is excreted in the urine in 6 hr by glomerular filtration and tubular secretion. Urinary concentration above 300 μg/ml have been reported after a dose of 250 mg (Tripathi, 2004).

**Antimicrobial Spectrum:** - It resembles benzyl penicillin in its action against gram (+) ve organisms including *Streptococcus pneumoniae* and other *Streptococci*. The gram (-) ve cocci moraxella, branhammelia, catarrhahatis, *Nesseria gonorrhoeae* and *N. meningitidis* are sensitive. It is more active than benzyl penicillin against some gram (-) ve bacilli including Haemophilus influenza and Enterobactereaceae such as *Escherichia coli, Proteus mirabilis, Salmonella and Shigella*. It is inactive against *Pseudomonas aeruginosa*.

Minimum inhibitory concentration (MIC) for sensitive Gram (+) ve organisms have been reported to range from 0.022-1.5μg/ml and for Gram (-) ve organisms from 0.03 to 3μg/ml. It is inactivated by β lactemases and complete cross resistance has been reported between AMOX and ampicillin. The spectrum of activity of AMOX may be extended by the concomitant use of β lactemase inhibitors such as clavulanic acid.

**Dose:** (Trihydrate equivalent) Oral: Adult and children weighing 20 kg or more: 250 to 500 mg every 8 hr but much as 4.5g day may be given if necessary for gonorrhoea.

- Infant 8 to 20 kg: 67 to 133 mg/kg every 8hrs
- Infants less than 8 kg: 35 to 50mg every 8hr.
- Infant 6 to 8 kg: 80 to 100mg every 8 hr.
Table: 3.2 Marketed products of Amoxycillin Trihydrate

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Dosage Form</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphamox</td>
<td>Alpha drugs &amp; Pharma</td>
<td>Tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>Amoxil</td>
<td>German Remedies</td>
<td>Capsule</td>
<td>250 mg</td>
</tr>
<tr>
<td>Amoxipen</td>
<td>PCI</td>
<td>Capsule</td>
<td>250 mg</td>
</tr>
<tr>
<td>Amoxivan</td>
<td>Khandelwal</td>
<td>Capsule</td>
<td>250 mg</td>
</tr>
<tr>
<td>Loxyn</td>
<td>AFD</td>
<td>Capsule</td>
<td>250 mg</td>
</tr>
<tr>
<td>Tormoxin</td>
<td>Torrent</td>
<td>Capsule</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

**Analytical methods of amoxicillin trihydrate:**

- Canals and Coldero (1997) have utilized the thin layer chromatography for the separation and identification of amoxicillin.

- Rao et al., (1986) preformed the spectrophotometric estimation of amoxicillin in formulation. The absorbance was measured at 440 nm.

- Mori et al., (1985) reported a fluorimetric method for determination of amoxicillin with mercurochrome. Fluorimetric determination was made at 535 nm.

- Bundgaard (1983) reported a new spectrophotometric method for selective determination of amoxicillin in the presence of polymers and other degradation products. The measurement was done at $\lambda_{\text{max}}$ 322 nm.

- Sane et al., (1983) and Jonkman and schoenmakes (1985) have described the determination of amoxicillin in plasma by ion pair high performance liquid chromatography.

- Rao et al., (1982) have described the colorimetric method for the estimation of amoxicillin. The absorbance measured at 480 nm.

- Brooks et al., (1981) reported an HPLC method for determination using amperiometric detector. Good linearity ($r = 0.9993$) was exhibited over the cited range by the amperiometric detector.