3. DRUG PROFILES

3.1. CLARITHROMYCIN

![Structure of clarithromycin](image)

**Fig. 3.1. Structure of clarithromycin**

3.1.1. Synonym

- 6-\(O\)-Methylerythromycin

3.1.2. Chemical name, molecular weight and CAS number

- \((2R, 3S, 4S, 5R, 6R, 8R, 10R, 11R, 12S, 13R)-3-(2,6-Dideoxy-3-C,3-O-dimethyl-\(\alpha\)-L-ribohexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-examethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-\(\beta\)-D-xylohexopyranosyloxy) pentadecan-13-olide

- \(C_{38}H_{69}NO_{13}\)=748.0

- CAS—81103–11–9

3.1.3. Description

- A white to off white crystalline powder. Crystals, Melting Point (M.P.) 217 to 220 °C if crystallized from chloroform and di-isopropyl ether; M.P. 222 to 225 °C from ethanol. It is practically insoluble in water; soluble in acetone; slightly soluble in acetonitrile, ethanol, and methanol.
3.1.4. Pharmacokinetics

- **Absorption**: Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration with a bioavailability of about 50-55%. Clarithromycin is highly stable in the presence of gastric acid. The relatively lower bioavailability is due to the first pass metabolism effect which produces the 14-hydroxyclarithromycin (Fraschini et al., 1991).

- **Drug Concentration Levels**: Time to peak concentration: oral: 2 to 4 h. Following a 250 mg dose, the $C_{\text{max}}$ ranges from 0.58 to 1.1 mg L$^{-1}$. After a 1200 mg dose, the $C_{\text{max}}$ ranges from 2.66 to 4.66 mg L$^{-1}$ (Fraschini et al., 1993).

- **Steady state (SS) peak serum clarithromycin concentration** in non-fasting healthy subjects is achieved within 3 days of oral dosing. The SS peak serum clarithromycin concentration is as follows: 1 to 2 µg mL$^{-1}$ with a 250 mg oral dose every 12 h; 3 to 4 µg mL$^{-1}$ with a 500 mg dose every 8 to 12 h.

- **Distribution and protein binding**: About 42 to 50% of clarithromycin is bound to plasma proteins. In plasma, about 80% at therapeutic concentrations i.e., free clarithromycin fraction increases at serum concentrations >1 mg mg L$^{-1}$ suggesting saturation of binding process. Clarithromycin is widely distributed into most body tissues with the exception of the central nervous system. It shows excellent gastric tissue distribution. Clarithromycin 500 mg every 8 hours in healthy adult males (n=5) results in the following average tissue concentrations: antrum 10.48 µg g$^{-1}$, fundus 20.81 µg g$^{-1}$, and mucus 4.15 µg mL$^{-1}$. If combining clarithromycin with omeprazole (40 mg daily), tissue and mucus drug concentrations increase as follows: antrum 19.96 µg g$^{-1}$, fundus 24.25 µg g$^{-1}$, and mucus 39.29 µg mL$^{-1}$. Volume of distribution is 243 to 266 L and its hydroxy metabolite is 304 to 309 L (Fraschini et al., 1993).

- **Metabolism**: Clarithromycin undergoes extensive metabolism in the liver by demethylation, hydroxylation and hydrolysis and the hydroxyl metabolite, 14-hydroxyclarithromycin, is active and a steady state concentrations of the
metabolite are reached within 2 to 3 days. It acts synergistically to increase the potency of the parent compound.

- **Excretion** The major route of clarithromycin clearance is through renal route. About 20 to 40% clarithromycin is excreted in the urine which is dose dependent, thus suggesting that metabolism may be saturable at higher doses. The renal clearance rate is 114 to 203 mL min\(^{-1}\) and the total body clearance is 29.2 to 58.1 L h\(^{-1}\). Approximately 10% to 15% of the principal metabolite (14-hydroxyl clarithromycin) is excreted in the urine when dosing clarithromycin as 250 or 500 mg every 12 h. Only small amounts of clarithromycin are excreted in bile and feces (Ferrero et al., 1990b).

- **Elimination half life:** Plasma half life is dose dependent: clarithromycin about 3 to 4 h in subjects taking 250 mg twice daily and about 5 to 7 h in subjects taking 500 mg twice daily; 14–hydroxyclarithromycin 5 to 6 h in subjects taking 250 mg twice daily and about 7 h in subjects taking 500 mg twice daily. The elimination half-life of clarithromycin is 3 to 7 h (Ferrero et al., 1990b). Elimination half life of the metabolite 14-hydroxyclarithromycin, is 5 to 9 h regardless of the dosing schedule.

### 3.1.5. Dose

- Clarithromycin is a macrolide, orally absorbed, broadspectrum antibiotic. It is widely used in a standard eradication treatment of gastric *H. pylori* infection combined with a second antibiotic and an acid suppressing agent. Clarithromycin has highest rate of eradication of *H. pylori* in monotherapy *in vivo*, though it is unstable and rapidly undergo degradation in low pH of gastric acid (Myung et al., 2005).

- The dose is 250 or 500 mg twice daily.

### 3.1.6. Ultraviolet Spectrum

- Aqueous acid (0.2 M H\(_2\)SO\(_4\))—283 nm; basic—282 nm.

### 3.1.7. Infra red Spectrum

- Principal peaks at wavenumbers 1052, 1170, 1108, 1734 cm\(^{-1}\) (KBr pellet).
3.1.8. High performance liquid chromatography

- System HBA—retention time 15.7 min; system HBB—retention time 6.8 min.
- Column: (analytical) C\textsubscript{18} (Nucleosil 100–3, 150 × 4.6 mm i.d., 3 μm); (pre-column) C\textsubscript{18} (Nucleosil 120–5, 10 × 4 mm, 5 μm) at 60°C. Mobile phase: methanol: 15 mM potassium dihydrogen phosphate buffer, adjusted to pH 6.0 with potassium hydroxide (70:30), 1.2 mL min\textsuperscript{-1} flow rate. UV detection (λ=220 nm). Retention time: 10.2 min (Macek et al., 1999).

- In plasma or urine: clarithromycin and 14–hydroxyclarithromycin, limit of detection 0.03 mg L\textsuperscript{-1}, electrochemical detection (Chu et al., 1991)

- In serum: limit of detection 0.2 mg L\textsuperscript{-1}, fluorescence detection, λ\textsubscript{ex}=255 nm, λ\textsubscript{em} = 315 nm (Torano and Guchelaar 1998).

- In plasma: limit of detection 0.03 mg L\textsuperscript{-1}, electrochemical detection (Kees et al., 1998)

- In plasma: limit of quantification is 0.1 mg L\textsuperscript{-1}, electrochemical detection (Taninaka et al., 2000).

- In plasma: limit of quantification 0.5 mg L\textsuperscript{-1}, UV detection (λ=220 nm) (Macek et al., 1999)
3.2. PANTOPRAZOLE SODIUM SESQUIHYDRATE

![Structure of Pantoprazole](image)

Fig. 3.2. Structure of Pantoprazole

3.2.1. Synonym(s)
- Pantoprazole sodium

3.2.2. Chemical name, Molecular weight and CAS number
- 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-enziimidazole
- $C_{38}H_{69}NO_{13}=432.4$
- CAS—164579-32-2

3.2.3. Description
- Pantoprazole sodium sesquihydrate an off white crystalline hygroscopic powder. Pantoprazole sodium sesquihydrate sample was found to be soluble in water, acetone, ethyl acetate, isopropanol, chloroform, ethanol and methanol. The melting point of pantoprazole sodium sesquihydrate was found to be 195 °C.

3.2.4. Pharmacokinetics
- **Absorption:** Pantoprazole is rapidly degraded in the acid environment of the stomach and is therefore administered as an enteric coated, delayed-release tablet (Andersson, 1996). Absorption begins only after the tablet passes through the stomach. Pantoprazole undergoes little first-pass metabolism, with an estimated absolute oral bioavailability of 77 % (Pue et al., 1993).
Drug concentration levels: maximum serum concentrations \( (C_{\text{max}}) \) are achieved 2 to 3 h after an oral dose (Hartmann et al., 1996; Huber, et al., 1996, & Tanaka et al., 1996).

After oral (Tanaka et al., 1996) and IV (Bliesath et al., 1994) administration of pantoprazole at single doses ranging from 10 to 120 mg, a good linear correlation was seen between the dose administered and the \( C_{\text{max}} \), as well as the area under the concentration-time curve. Serum concentrations obtained after multiple doses are not significantly different from those obtained after the initial dose (Hartmann et al., 1996, & Tanaka et al., 1996).

**Distribution:** Distribution sites and protein binding: plasma protein binding is 98% (Fitton and Wiseman, 1996; Huber et al., 1996, & Pue et al., 1993).

Distribution Kinetics: Reported volumes of distribution range from 0.15 to 0.17 L kg\(^{-1}\), suggesting localization of a major fraction of pantoprazole within the extracellular water (Fitton and Wiseman, 1996; Huber et al., 1996, & Pue et al., 1993).

**Metabolism:** Plasma protein binding is 98%. Reported volumes of distribution range from 0.15 to 0.17 L kg\(^{-1}\), suggesting localization of a major fraction of pantoprazole within the extracellular water (Fitton and Wiseman, 1996; Huber et al., 1996, & Pue et al., 1993).

Pantoprazole is extensively metabolized by the liver, with little unchanged drug excreted in the urine (Tanaka et al., 1996; Bliesath et al., 1994; Pue et al., 1993, & Meyer, 1996).

Metabolism to the inactive metabolite hydroxypantoprazole occurs primarily via the cytochrome P, CYP 2C19 isozyme, followed by sulfate conjugation and some sulfone or sulfide formation (Meyer, 1996, & Tanaka et al., 1997). CYP3A4 facilitates some sulfone and sulfide formation from the parent drug.

**Excretion:** Approximately 80% of an oral or IV dose is excreted in the urine as Pantoprazole metabolites, with the remainder excreted in the feces via biliary secretion (Huber, et al., 1996).
• **Elimination half-life**: Elimination half life has ranged from 0.9 to 1.9 h (Fitton and Wiseman, 1996; Hartmann et al., 1996; Huber et al., 1996; Tanaka et al., 1996, & Pue et al., 1993).

• Elimination half life and plasma clearance of Pantoprazole have been shown to be independent of dose (Huber, et al., 1996, & Bliesath, et al., 1994).

• **Clearance**: In various studies, mean or median clearance of pantoprazole has ranged from 0.7 to 1.3 L kg\(^{-1}\) h\(^{-1}\) (Unge, 1997).

### 3.2.5. Pharmacodynamics

Pantoprazole exerts its pharmacodynamic actions by inhibiting H\(^+\),K\(^+\)-adenosine triphosphatase (H\(^+\),K\(^+\)-ATPase), the proton pump, which is the terminal step in acid secretion by the parietal cells of the gastric mucosa.

![Fig. 3.3. Mechanism of gastric acid suppression through different pathways](image)

(Okbe et al., 2003)

PPIs are substituted benzimidazoles that accumulate in the highly acidic environment of the parietal cell canalicular lumen and are activated by conversion to cyclic sulfenamides. The activated sulfonamides subsequently inactivate proton
pumps by covalently binding to cysteine residues. The binding of PSS to proton pumps is irreversible. Like other PPIs, pantoprazole exerts its pharmacodynamic actions by inhibiting H+,K+-adenosine triphosphatase (H+,K+-ATPase), the proton pump, which is the terminal step in acid secretion by the parietal cells of the gastric mucosa (Shin et al., 1994; Sachs 1997; Sachs et al., 1994; Huber et al., 1996; Kromer 1990, & Fitton and Wiseman, 1996).

PPIs are substituted benzimidazoles that accumulate in the highly acidic environment of the parietal-cell canalicular lumen and are activated by conversion to cyclic sulfonamides (Kromer, 1990, & Fitton and Wiseman, 1996). The activated sulfonamides subsequently inactivate proton pumps by covalently binding to cysteine residues. With the possible exception of rabeprazole, the binding of PPIs to proton pumps is irreversible. Thus, the life of proton pumps and the time required for the regeneration of new pumps are the primary factors controlling the duration of pharmacodynamic effect of this class of drugs. Regeneration generally requires about 96 hours in humans (Kromer, 1990).

3.2.6. Dose

- Pantoprazole appears to be effective in the eradication of *H. pylori* when combined with appropriate antibiotics. A dose of 40 mg BID or 80 mg d⁻¹ may be more effective for this purpose than 40 mg d⁻¹.

- Pantoprazole has been shown to be at least as effective as omeprazole in clinical studies in patients with gastric and duodenal ulcers. Rates of *H pylori* eradication were similar when pantoprazole, omeprazole, or lansoprazole was given as part of a regimen including 2 antibiotics. Pantoprazole may have some advantage over other PPIs in that it seems to lack the potential for drug interactions mediated by inhibition or induction of CYP2C19, CYP3A4, or other CYP450 isozymes. This characteristic may prove particularly useful in patients taking multiple drugs (Jungnickel, 2000).

- Pantoprazole at dosages ranging from 40 to 80 mg d⁻¹ has been combined with 2 antibacterial agents in 7-14 days regimens for the eradication of *H. pylori*. In clinical studies Pantoprazole at dosages ranging from 40 to 80 mg d⁻¹ has been
combined with 2 antibacterial agents in 7-14 day regimens for the eradication of *H. pylori* (Jungnickd, 2000).

- LD50 (rat, SC): 7.5 g kg\(^{-1}\)

**3.2.7. Ultraviolet spectrum**

- Water — 225 nm and 290 nm.

**3.2.8. Infra–red spectrum**

- IR spectra of pantoprazole sodium show significant \(-\text{O}-\text{H}\) and \(-\text{C}-\text{H}\) absorption bands from 3000 to 3500 cm\(^{-1}\); \(\text{C-C, C-N}\) absorption bands from 1800 to 1500 cm\(^{-1}\) (Badwan et al., 2002). Sesquihydrate has an absorption band at 815 cm\(^{-1}\).

**3.2.9. High performance liquid chromatography**

- System: HPLC (Perkin-Elmer series200); retention time 6.8 min.; Column: Waters Nova Pak column C18 (150 mm); Mobile phase: acetonitrile/phosphate buffer (35:65 v/v), pH 7.4 (Raffin et al., 2006).