CHAPTER 4
DRUG PROFILE
4. DRUG PROFILE

4.1. Nelfinavir mesylate

Nelfinavir mesylate is official in Indian Pharmacopoeia

**General Name:** Nelfinavir mesylate

**Chemical Structure:**

![Chemical Structure Image]

**Chemical Name:** $(3S,4aS,8aS)-N$-tert-buty1-2-((2R,3R)-2-hydroxy-3-(3-hydroxy-2 methylbenzamido)-4-(phenylthio)butyl)decahydroisoquinoline-3-carboxamide methanesulfonate

**Molecular Formula:** $C_{32}H_{45}N_3O_4S$

**Molecular Weight:** 663.9

**Melting Point:** 349.94 °C

**Description:** A white or almost white powder

**pKa:** 6.00, 11.06

**Solubility:** Slightly soluble in water and freely soluble in methanol, ethanol and 2-propanol.

**Drug Category:** Antiretroviral
Clinical Pharmacology:
Nelfinavir is a nonpeptidic protease inhibitor that is active against both HIV-1 and HIV-2 and is formulated as the mesylate salt of a basic amine [106]. Nelfinavir reversibly binds to the active site of the HIV protease, preventing polypeptide processing and subsequent virus maturation. This protease is an enzyme which cleaves viral protein molecules into smaller fragments, and it is vital for both the replication of the virus within the cell and also the release of mature viral particles from an infected cell. Though this mode of action is common to all protease inhibitors, the precise mode of binding of nelfinavir to the enzyme may be sufficiently unique to reduce cross-resistance between it and other PIs. Also, not all PIs inhibit both HIV-1 and HIV-2 proteases.

Pharmacokinetics:
Nelfinavir is absorbed more slowly than other HIV-1 protease inhibitors, with peak concentrations achieved in 2 to 4 hours. As a result, drug concentrations continue to fall for 2 to 3 hours after taking the next dose of drug. Nelfinavir absorption is very sensitive to food effects; a moderate-fat meal increases the AUC two- to threefold, and higher concentrations are achieved with high-fat meals. Nelfinavir undergoes oxidative metabolism in the liver primarily by CYP2C19 but also by CYP3A4 and CYP2D6. Its major hydroxy-\(t\)-butylamide metabolite, M8, is formed by CYP2C19 and has in vitro antiretroviral activity similar to that of the parent drug. This is the only known active metabolite of an HIV protease inhibitor. M8 concentrations are 30% to 40% those of parent drug. Nelfinavir and its metabolites are eliminated primarily in feces, with less than 2% of drug excreted unchanged in the urine. Moderate or severe liver disease may prolong the half-life and increase plasma concentrations of the parent drug while lowering plasma concentrations of M8. Nelfinavir is greater than 98% bound to plasma proteins, mostly to albumin and \(\alpha_1\)-acid glycoprotein. It is present in CSF at less than 1% of plasma concentrations [107].

Toxicity:
Nelfinavir is generally well tolerated but some common adverse reactions include diarrhea or loose stools, nausea, flatulence and skin rash.
4.2. Linezolid

Linezolid is official in Indian Pharmacopoeia

General Name: Linezolid

Chemical Structure:

![Chemical Structure Diagram]

Chemical Name: N-[(5S)-3-(3-fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl]acetamide

Molecular Formula: C_{16}H_{21}N_{3}O_{4}F

Molecular Weight: 337.4

Melting Point: 181.5-182.5 °C

Description: A white to off-white crystalline powder

pKa: 1.8

Solubility: Freely soluble in methanol, ethanol and acetonitrile and practically insoluble in water

Drug Category: Anti-Infective Agent

Clinical Pharmacology:

Linezolid is a synthetic antimicrobial agent of the oxazolidinone class, used for the treatment of infections caused by multi-resistant bacteria including streptococcus and methicillin-resistant Staphylococcus aureus (MRSA). The drug works by inhibiting the initiation of bacterial protein synthesis. Linezolid inhibits protein synthesis by binding to the P site of the 50S ribosomal subunit and preventing formation of the larger ribosomal-fMet-tRNA
complex that initiates protein synthesis. As mentioned above, there is no cross-resistance with other drug classes. Resistance in enterococci and staphylococci is due to point mutations of the 23S rRNA. Since multiple copies of 23S rRNA genes are present in bacteria, resistance generally requires mutations in two or more copies.

**Pharmacokinetics:**
Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite.

**Toxicity:**
The drug seems to be well tolerated, with generally minor side effects (e.g., gastrointestinal complaints, headache, rash). Myelosuppression, including anemia, leukopenia, pancytopenia, and thrombocytopenia, has been reported in patients receiving linezolid. Clinical signs of acute toxicity lead to decreased activity, ataxia, vomiting and tremors [108].
4.3. Lacosamide

Lacosamide is a Non-Pharmacopoeial drug

**General Name:** Lacosamide

**Chemical Structure:**

![Chemical Structure of Lacosamide](image)

**Chemical Name:** (R)-2-acetamido-N-benzyl-3-methoxypropionamide

**Molecular Formula:** $C_{13}H_{18}N_2O_3$

**Molecular Weight:** 250.3

**Melting Point:** 140-146 °C

**Description:** A white to light yellow powder

**pKa:** 5.0

**Solubility:** Freely soluble in methanol, ethanol and acetonitrile, very slightly soluble in water.

**Drug Category:** Antiepileptic Agent.

**Clinical Pharmacology:**

Lacosamide is a novel glycine-site NMDA ($N$-methyl-$D$-aspartic acid) receptor antagonist, used for the treatment of both epilepsy and diabetic neuropathic pain. It is a member of family of functionalized amino acids, more specifically, analogues of endogenous amino acid and NMDA-receptor modulator D-serine [109]. Lacosamide is a functionalized amino acid that has activity in the maximal electroshock seizure test, like antiepileptic drugs that are believed to act through voltage-gated sodium channels. However, lacosamide does not
act in a conventional way to stabilize fast sodium channel inactivation. Rather, recent studies indicate that it enhances slow inactivation. During an action potential voltage gated sodium channels undergo fast inactivation. This inactivation prevents the channel from opening, and helps end the action potential.

**Pharmacokinetics:**
Absorption of lacosamide is rapid and is widely distributed in the body. It undergoes metabolism in liver and excreted via kidney. Less than 15% of the drug remains in protein bound state and almost 40% of the drug is excreted unchanged in the urine. Lacosamide undergoes oxidative biotransformation in the presence of CYP-450 enzyme system and the other metabolic pathway involves glucuronidation and hydroxylation [110].

**Toxicity:**
Lacosamide is generally well tolerated in adult patients with partial-onset seizures. Dizziness is the most common treatment-related adverse event. Some of the other dose dependent toxic responses include nausea, tremor, fatigue, vomiting etc.
4.4. Ritonavir

Ritonavir is official in Indian Pharmacopoeia and United States Pharmacopoeia

**General Name:** Ritonavir

**Chemical Structure:**

![Chemical Structure of Ritonavir](image)

**Chemical Name:** \([5S,8S,10S,11S])-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid-5-thiazolylmethyl ester

**Molecular Formula:** C\(_{37}\)H\(_{48}\)N\(_6\)O\(_5\)S\(_2\)

**Molecular Weight:** 720.9

**Melting Point:** 120-123 °C

**Description:** A white or almost white powder

**pKa:** 3.48

**Solubility:** Freely soluble in methanol and in methylene chloride; very slightly soluble in acetonitrile; practically insoluble in water.

**Drug Category:** Antiretroviral (HIV Protease Inhibitor)
Clinical Pharmacology:
Ritonavir reversibly binds to the active site of the HIV protease, preventing polypeptide processing and subsequent virus maturation. HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1. Ritonavir binds to the protease active site and inhibits the activity of the enzyme. Virus particles are produced in the presence of ritonavir but are noninfectious.

Pharmacokinetics:
Absorption of ritonavir is rapid and is only slightly affected by food, depending on the formulation. The overall absorption of ritonavir from the capsule formulation increases by 13% when the capsule is taken with meals, but the bioavailability of the oral solution decreases by 7%. Interindividual variability in pharmacokinetics is high, with a greater than six-fold variability in trough concentrations among patients given 600 mg twice daily. There are almost five metabolites have been identified. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of ritonavir, however, plasma concentrations are low. The cytochrome P-450 enzymes CYP3A and CYP2D6 are primarily involved in the metabolism of ritonavir. Ritonavir and its metabolites are mainly eliminated in feces (86% of parent drug and metabolites), with only 3% of drug eliminated unchanged in the urine. Ritonavir is 98% to 99% bound to plasma proteins, mainly to $\alpha_1$-acid glycoprotein [111].

Toxicity:
The major side effects of ritonavir are gastrointestinal and include nausea, vomiting, diarrhea, anorexia, abdominal pain, and taste perversion. These side effects are dose-dependent and are less common with lower doses. Gastrointestinal toxicity may be reduced if the drug is taken with meals. Peripheral and perioral paresthesias also are common [112].