4.1 Paclitaxel

Paclitaxel 1 is a natural product with antitumor activity. Paclitaxel was not a chance discovery but was the outcome of the investigation of over 12,000 natural compounds for anti-cancer activity (Appendino, 1993). It was discovered in a U.S. National Cancer Institute program at the Research Triangle Institute in 1967 when Monroe E. Wall and Mansukh C. Wani isolated it from the bark of the Pacific yew tree, *Taxus brevifolia* and named it taxol. When it was developed commercially by Bristol-Myers Squibb (BMS) the generic name was changed to paclitaxel and the BMS compound is sold under the trademark Taxol. In this formulation, paclitaxel is dissolved in Cremophor EL and ethanol, as a delivery agent. (Wikipedia.org; Wani *et al*., 1971). Paclitaxel is now used to treat patients with lung, ovarian, breast, head and neck cancer, and advanced forms of Kaposi's sarcoma. Paclitaxel is also used for the prevention of restenosis.

IUPAC Name

5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxymtax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenyllisoserine

CAS Number

33069-62-4

Molecular Formula

C_{47}H_{51}NO_{14}
Molecular Weight
853 Da

Description
Paclitaxel is white to off white crystalline powder.

Solubility
Practically insoluble in water, soluble in methanol and freely soluble in methylene chloride.

Partition Coefficient
3.62

Melting Point
216-217 °C

Storage
Store the drug between 20-25 °C in light resistant container.

4.2 Mechanism of Action
Paclitaxel stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules during cell division. The microtubule formed in the presence of paclitaxel are extraordinary stable and dysfunctional, thereby causing the death of the cell by disrupting the normal tubule dynamics. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division. Unlike other tubulin-targeting drugs such as colchicine that inhibit microtubule assembly, paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks progression of mitosis, and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division (Bharadwaj et al., 2004; Brito et al., 2008) Figures 4.1 and 4.2 show the mechanism of action of paclitaxel.
Figure 4.1: Mechanism of action of paclitaxel in cancer cell life cycle

Figure 4.2: Complex of α, β tubulin subunits and paclitaxel. Paclitaxel is shown as yellow stick (Source wikipedia.org)
4.3 Pharmacokinetic Profile

Pharmacokinetic parameters of paclitaxel (Sonnichsen et al., 1994).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Oral bioavailability (%)</td>
<td>10-15</td>
</tr>
<tr>
<td>2.</td>
<td>Urinary excretion (%)</td>
<td>5.0±2</td>
</tr>
<tr>
<td>3.</td>
<td>Bound in plasma (%)</td>
<td>88-98</td>
</tr>
<tr>
<td>4.</td>
<td>Clearance (mL/min/kg)</td>
<td>5.5±3.5</td>
</tr>
<tr>
<td>5.</td>
<td>Vol. dist. (liters/kg)</td>
<td>2.0±1.2</td>
</tr>
<tr>
<td>6.</td>
<td>Half life (h)</td>
<td>3.0±1</td>
</tr>
<tr>
<td>7.</td>
<td>Peak concentration (µM)</td>
<td>0.85±0.21</td>
</tr>
</tbody>
</table>

4.4 Therapeutic Uses

The efficacy of paclitaxel confirmed in ovarian cancer, breast cancer, head and neck cancer, small cell lung cancer, multiple myeloma, melanoma and Kaposi’s sarcoma. It is approved by USFDA for the treatment of ovarian, breast, lung cancers and AIDS related Kaposi’s sarcoma. Similarly paclitaxel is also approved in the UK for ovarian, breast, lung cancers and AIDS related Kaposi's sarcoma (Savile et al., 1995).

Paclitaxel is used as an antiproliferative agent for the prevention of restenosis (recurrent narrowing) of coronary stents; locally delivered to the wall of the coronary artery, a paclitaxel coating limits the growth of neointima (scar tissue) within stents (Heldman et al., 2001). Paclitaxel drug eluting coated stents are sold under the trade name Taxus by Boston Scientific in the United States.

4.5 Adverse Effects

The major toxicities of paclitaxel are neutropenia, mucositis, neurotoxicity, hypersensitivity. Some of side effects related to different organs of human body are as follows:

Cardiovascular - Ventricular tachycardia, atrial arrhythmias, ischemia, asymptomatic bradycardia and atrioventricular conduction blocks
**Chapter 4 - Drug profile**

**Hematological** - Neutropenia, thrombocytopenia

**Hypersensitivity** - Dyspnea with bronchospasm, urticaria, hypotension

**Neurotoxicity** - Peripheral neuropathy, transient myalgia, scintillating scotomata

**Gastrointestinal tract** - Mucosities, nausea, vomiting, diarrohea

**Hepatotoxicity** - Elevation of Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT)

**Hair** - Alopecia

**Nails** - Onycholysis

**Others** - Myopathy, fatigue, pulmonary lipid embolism

### 4.6 Contraindications

Cremophor EL based marketed formulation is contraindicated in patients who have a history of hypersensitivity reactions.

### 4.7 Dose

Paclitaxel is generally given at a dose of 135 or 175 mg/m² as a 3- or 24 h infusion every three weeks. The maximum tolerated dose (MTD) of paclitaxel administrated by 3 h infusion to patients with solid tumors was found to be 225-240 mg/m² without any hypersensitivity reactions but resulted in hypotension (Kramer Heuser, 1995). Paclitaxel injectable formulation TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials.

### 4.8 Drug Over Dose

There is no known antidote for paclitaxel over dosage. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

### 4.9 Drug Interactions

The major pharmacodynamic interaction of paclitaxel is with other cytostatic drugs. But significant pharmacokinetic interactions may also occur. The drugs that inhibit or induce the cytochrome P450 isoenzymes would be expected to alter the metabolism of paclitaxel. *In vitro* ranitidine, diphenhydramine, vincristine, vinblastine and doxorubicin
little or no effect on the metabolism of paclitaxel, but barbiturates stimulated hydroxylation of the side chain by induction of CYP3A4 isoforms.

### 4.10 Pharmacopeial Status

<table>
<thead>
<tr>
<th>Pharmacopeia</th>
<th>Monographs</th>
<th>Page No</th>
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<tr>
<td>Indian Pharmacopeia 2007</td>
<td>Paclitaxel and paclitaxel Injection</td>
<td>Vol III, 897</td>
</tr>
<tr>
<td>British Pharmacopeia 2009</td>
<td>Paclitaxel</td>
<td>4505</td>
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Table 4.1: Commercially available dosage forms of paclitaxel.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Dosage Form</th>
<th>Brand Name</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Injection Solution</td>
<td>Dayls</td>
<td>Laboratorio, DOSA, Argentine</td>
</tr>
<tr>
<td>2.</td>
<td>Lyophilized powder for injection</td>
<td>Abraxane</td>
<td>Abraxis Bioscience, Los Angeles, CA</td>
</tr>
<tr>
<td>3.</td>
<td>Injection</td>
<td>Taxol</td>
<td>Bristol-Myers Squibb Company, New Jersey, USA</td>
</tr>
<tr>
<td>4.</td>
<td>Polymeric nanoparticles</td>
<td>Nanoxel</td>
<td>Dabur India Ltd, India</td>
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