VALIDATED BIOANALYTICAL METHOD

# Bioanalytics, Metabolomics and Pharmacokinetics Shared Resource (BMPK)

# Docetaxel in Heparinized Human Plasma

**(Sensitivity: 0.200 ng/mL)**

**BMPK has validated a highly sensitive HPLC assay with tandem mass spectrometric detection (LC-MS/MS) for the analysis of docetaxel (Taxotere®) in heparinized human plasma. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells, which is essential for mitotic and interphase cellular functions.[1] Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. *In vitro* drug interaction studies have shown that docetaxel is metabolized by the CYP3A4 isoenzyme and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine.[1] Based on these *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. Currently, it is approved alone or in combination with other agents for locally advanced or metastatic breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer.**

## Specifications and Validation Performance

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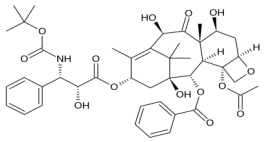
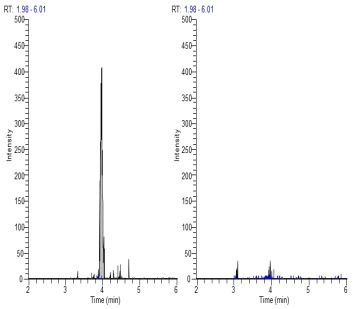
|---|---|
| **Matrix (Anticoagulant):** | **Human Plasma (Sodium Heparin)** |
| **Sample Volume:** | **200 µL** |
| **Preparation Procedure:** | **Liquid / liquid extraction** |
| **HPLC Column:** | **C18** |
| **Mobile Phase:** | **Acetonitrile with Ammonium Acetate** |
| **Flow Rate:** | **200 µL/min** |
| **Detection Type:** | **Tandem Mass Spectral Analysis (MS/MS)** |
| **Calibration Range:** | **0.200 - 400 ng/mL** |
| **Calibrator Accuracy:** | **100% (93.6 - 108%; n=5)** |
| **Calibrator Precision:** | **2.56% CV (1.42 - 4.84%; n=5)** |
| **QC Concentrations:** | **0.750, 15.0 and 300 ng/mL** |
| **QC Accuracy:** | **105% (104 - 105%; n=18)** |
| **QC Precision:** | **4.45% CV (3.75 - 5.13%; n=18)** |



**Docetaxel**
**Formula: $C_{43}H_{53}NO_{14}$**
**MW: 807.88 g/mol**




## Human Pharmacokinetic Parameters of Docetaxel[1,2,3]

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|---|---|
| **Single Agent Recommended Dosing** | **60-100 mg/m$^2$ IV qw followed by 7 day rest; dependent on disease type and prior treatment** |
| **Single Agent Maximum Tolerated Dose (MTD)** | **>125 mg/m$^2$ IV qw followed by 7 day rest, dependent on disease type and prior treatment** |
| **Active Metabolites** | **None** |
| **Metabolism** | **75% excreted in feces and 6% in urine after 7 days as oxidized metabolites (>8% as unchanged drug)** |
| **Plasma Protein Binding** | **94% *in vitro*, 97% *in vivo*** |
| **Overall Exposure by Area Under the Curve (AUC)** | **Dose proportional from 70-115 mg/m$^2$ using a three-compartment pharmacokinetic model** |
| **Major Adverse Reactions** | **Hepatoxicity, neutropenia, hypersensitivity, fluid retention** |

[1]Patient Information Leaflet for Taxotere, Aventis Pharmaceuticals, Inc., Revision. May 2004; [2]CDER Application Number NDA 20-449/S-035, Approved March 22, 2006; and [3]Clinical Pharmacokinetics of Docetaxel, Clin Pharmacokinet, 45 (3), 2006.

**BMPK offers a wide range of bioanalytical and PK/PD modeling services to assist investigators with their basic research, preclinical, and clinical study objectives. For information on services and pricing, contact Joshua Prey, MS, Research Project Administrator at (716) 845-3313 or Josua.Prey@RoswellPark.org.**

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