

# Bioanalytics, Metabolomics and Pharmacokinetics Shared Resource (BMPK)

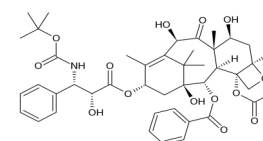
Director: Dr. James Mohler

## Docetaxel in Heparinized Human Plasma (Sensitivity: 0.200 ng/mL)

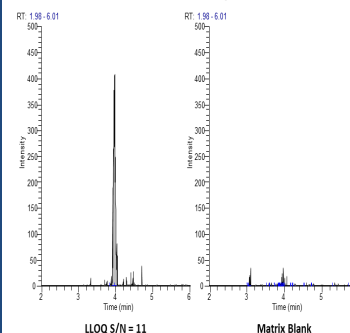
BMPK has validated a highly sensitive HPLC assay with tandem mass spectrometric detection (LC-MS/MS) for the analysis of docetaxel (Taxotere®) in heparinized human plasma. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells, which is essential for mitotic and interphase cellular functions.<sup>1</sup> 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.<sup>1</sup> 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

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



**Docetaxel**  
Formula: C<sub>43</sub>H<sub>53</sub>NO<sub>14</sub>  
MW: 807.88 g/mol



### Human Pharmacokinetic Parameters of Docetaxel<sup>1,2,3</sup>

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

<sup>1</sup>Patient Information Leaflet for Taxotere, Aventis Pharmaceuticals, Inc., Revision. May 2004; <sup>2</sup>CDER Application Number NDA 20-449/S-035, Approved March 22, 2006; and <sup>3</sup>Clinical Pharmacokinetics of Docetaxel, Clin Pharmacokinetics, 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 John Wilton, Ph.D., Associate Director, at (716) 845-3258 or John.Wilton@RoswellPark.org.

