

BO-007

## FORMULATION OF DOCETAXEL USING PRODRUGS FOR INTRAVENOUS DELIVERY

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### ABSTRACT

Docetaxel (Taxotere®) represents a novel class of antineoplastic drugs. Docetaxel (DTX) is an inhibitor of microtubule depolymerization and has a broad antitumor activity against a variety of solid tumors, including breast, non-small cell lung cancer, ovarian as well as gastric, head and neck, and prostate carcinomas. Unfortunately, however, docetaxel is a highly lipophilic white powder and practically insoluble in water. Due to its poor water solubility, docetaxel has been formulated in polysorbate 80 (Tween-80) which results in severe side effects. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients. Hypersensitivity reactions require immediate discontinuation of the Taxotere® infusion and administration of appropriate therapy. All the hypersensitive reactions mentioned above are primarily caused by and due to the presence of polysorbate 80 in the formulation. This study explores the use of prodrugs to affect improved parenteral delivery of poorly water-soluble problematic drugs, using both docetaxel as well as investigational prodrugs as examples. To improve the aqueous solubility of docetaxel for parenteral administration, prodrugs of the monosaccharides D-glucose (DTX-G), the disaccharides D-lactose (DTX-L), and the amino carbohydrates sialic acid (DTX-S) were prepared and evaluated for solubility. But DTX-G is chosen to be a potential drug because of its good biocompatibility. Improved solubility at combination cosolvents and combination surfactants was observed for prodrugs. The results showed that a PEG 400(15%, w/w) - polysorbate 80 (2.5%, w/w) - HP $\beta$ CD (20%, w/w) mixture in the parenteral formulations significantly increased the solubility (up to 5.0 mg/mL). These results demonstrate that it is possible to develop a parenteral aqueous solution of prodrug of docetaxel with less surfactant.

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