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P125. SILDENAFIL: TOXICITY AND ANALYSIS METHODS

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Sildenafil citrate (*1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo-[4,3-d]pyrimidin-5-yl) phenylsulphonyl]-4-methylpiperazine*) is widely prescribed for the treatment of pulmonary arterial hypertension (PAH) and impotence-male erectile dysfunction. Sildenafil citrate is a potent and selective inhibitor of cyclic guanosine monophosphate specific PDE5, and causes relaxation of smooth muscle, in particular, in the pulmonary vasculature and corpus cavernosum. Oral sildenafil is absorbed rapidly, reaching peak plasma concentrations after ≈1 hour. It is metabolized principally by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP2C9, and inducers or inhibitors of these isozymes can affect the clearance of sildenafil. Sildenafil is predominantly excreted as metabolites in the feces (≈80% of the administered oral dose), with ≈%13 excreted in the urine, and has a terminal elimination half-life of 3–5 hours. Sildenafil undergoes first-pass metabolism and the mean absolute bio- availability is ≈%41. The major (N-desmethyl) metabolite of sildenafil has an in vitro potency approximately half that of the parent compound. Because of its increasing popularity and potential side effects, the need for a procedure to detect both sildenafil and N-desmethyl sildenafil in biological samples is becoming increasingly important. Several high-performance liquid chromatographic (HPLC) methods have been reported for the determination of sildenafil and/or N-desmethyl sildenafil in biological samples. Gas chromatography–mass spectrometry (GC/MS), micellar electrokinetic chromatography, liquid chromatography–mass spectrometry (LC/MS) as well as liquid chromatography–tandem mass spectrometry (LC/MS/MS) methods have been reported.