Final Report

Study Title	(^{14}C)-XR-9576: Quantitative whole-body autoradiography following intravenous administration (10 mg free base/kg) to the pigmented rat
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SUMMARY

Objectives

This study was conducted in order to determine the distribution of radioactivity (using quantitative whole-body autoradiography) following intravenous administration of (^{14}C)-XR-9576.14 to male pigmented rats.

Methods

Rats were dosed once by intravenous infusion with (^{14}C)-XR-9576.14 at a nominal dose level of 10 mg base/kg body weight. Single animals were then killed by being plunged into a freezing mixture (containing an excess of dry-ice in hexane), following anaesthesia under Halothane^{TM}, at the following times after dosing:

- 2 and 6 hours and 1, 3, 7, 14 and 35 days

Once fully frozen, the carcasses were prepared for, and subjected to whole-body autoradiography procedures. Radioactivity concentrations in tissues were quantified from the whole-body autoradiograms, using a validated image analysis system.

Results

The radiolabelled test article (and/or its radiolabelled metabolites) was widely distributed in to the tissues following intravenous infusion of (^{14}C)-XR-9576.14. In almost all cases, the levels of radioactivity measured in the tissues were much higher than that present in the blood. Peak levels of radioactivity were attained in the majority of tissues at the first sampling time after dosing (2 hours) and then declined such that few contained measurable levels of radioactivity at 3 days post dose. In the majority of cases, tissue radioactivity declined quite rapidly after attainment of peak levels. However, there were a number of exceptions. Of particular note were the very high levels of radioactivity associated with the uveal tract of the eye and other melanin-rich pigmented tissues. Concentrations of radioactivity in these tissues (in particular the uveal tract: estimated elimination half-life 3538.5 hours) indicate a very high degree of melanin binding.

Inspection of the autoradiograms and analysis of the quantitative and qualitative data produced in this study indicates that radioactivity was widely eliminated in the faeces probably resulting from extensive biliary secretion of drug-related material and/or secretion of drug-related material across the intestinal mucosa.