

CARDIOVASCULAR EFFECTS OF MIXED MICELLES [REDACTED] 17-7465/001) IN CONSCIOUS NORMOTENSIVE RABBITS (REF III F5)

This study was performed in one NZW and two Burgund strain rabbits. Ro 17-7465/001 was administered IV at 0.66 ml/kg. There were no compound related effects on MAP but the HR increased moderately by 19% for approximately 12 min.

EFFECTS OF THE MIXED MICELLE SOLUBILISATE [REDACTED] 17-7465 ON SYSTOLIC ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS SPONTANEOUSLY HYPERTENSIVE (SHR) RATS (REFS III F5, III F6)

3 Male spontaneously hypertensive rats were examined after exposure to [REDACTED] 17-7465/001 or [REDACTED] 17-7465/002 at IV doses of 0.66 or 2.2 ml/kg. There were no significant changes in systolic or diastolic arterial pressure or heart rate.

EFFECTS OF THE MIXED MICELLE SOLUBILISATE [REDACTED] 17-7465 ON SYSTOLIC ARTERIAL BLOOD PRESSURE AND HEART RATE IN CONSCIOUS SPONTANEOUSLY HYPERTENSIVE (SHR) RATS (REFS III F5, III F6)

Study performed by [REDACTED] Dated June 14, 1984.
No GLP or QA statement was provided. [REDACTED] report number: B-101'465.

3 Male spontaneously hypertensive rats were examined after exposure to [REDACTED] 17-7465/001 or [REDACTED] 17-7465/002 at IV doses of 0.1, 0.3 and 1.0 ml/kg. There were no significant changes in systolic arterial pressure or heart rate.

EFFECTS ON THE RENAL SYSTEM

EFFECT OF [REDACTED] 17-7465 ON THE EXCRETION OF URINE AND ELECTROLYTES IN CONSCIOUS RATS AND DOGS (REF. III F7)

Study performed by [REDACTED] Dated July 10, 1984.
No GLP or QA statement was provided. [REDACTED] report number: B-101'468

EFFECT OF [REDACTED] 17-7465 ON THE EXCRETION OF URINE AND ELECTROLYTES IN RATS

10 Female rats/group were fasted for 16-18 h and injected IV with 0.01, 0.03, 0.1, 0.3 and 1.0 ml/kg of [REDACTED] 17-7465/001 or [REDACTED] 17-7465/002. Following the injection, animals were orally saline-loaded with 20 ml/kg. Urine was collected over a 5 h period. Urinary volume and total sodium and potassium excreted were calculated and compared with controls.

RESULTS: There was no effect on urine volume, sodium or potassium excretion at doses up to 0.3 ml/kg for either test agent. At 1.0 ml/kg, [REDACTED] 17-7465/001 produced a salidiuretic effect (increased volume, sodium and potassium excretion). At 1.0ml/kg, [REDACTED] 17-7465/002 produced only a small increase in potassium excretion.

EFFECT OF [REDACTED] 17-7465 ON THE EXCRETION OF URINE AND ELECTROLYTES IN DOGS (REF IIIIF7)

3 female Swiss beagle dogs/group were fasted overnight. IV injections of 0.01, 0.03, 0.1, 0.3 and 1.0 ml/kg of [REDACTED] 17-7465/001 and [REDACTED] 17-7465/002 were administered. Dogs were then saline-loaded with 5 ml/kg physiological saline. Urine was collected for six 60 minute periods. Urine volume and total sodium and potassium excreted were calculated and compared with controls.

RESULTS: There were no dose-related findings at 0.01 to 0.3 ml/kg. At 1.0 ml/kg, relative urine volume was increased markedly and the excretion of sodium was also increased; potassium excretion was not increased. (Interestingly, at the lower doses there was a slight retention of potassium, but this was deemed non-dose-related). Some dogs dosed with 0.3 or 1.0 ml/kg exhibited emesis.

EFFECTS ON THE GASTROINTESTINAL SYSTEM

[REDACTED] 17-7465/001 AND 17-7465/002: EXAMINATION ON GASTROINTESTINAL TRANSIT IN MICE

Study performed by [REDACTED] Dated August 20, 1985. No GLP or QA statement was provided. [REDACTED] report number: B-101'269

IV doses of 0.1, 0.5, 1.0, 2.0, 5.0 and 10.0 ml/kg were administered to 10-20 male mice/group. 30 minutes later, 0.5 ml of a colored PVC suspension in tragacanth was orally administered. Animals were sacrificed 3.5 h later. A comparison was made by calculating the number of mice without marker in the caecum compared to controls.

RESULTS: Neither formulation inhibited g.i. transit up to 1.0 ml/kg. 2ml/kg of fresh micelles resulted in moderate inhibition of transit while 5.0 ml/kg completely inhibited transit. 10 ml/kg was 90% lethal. [REDACTED] 17-7465/002 moderately inhibited g.i. transit at 2 ml/kg; higher doses resulted in 6/20 rats dying. After 10 ml/kg of either compound, the animals died. These tests were performed to analyze the expected cathartic effect that bile acids have in humans. This effect was not evident in the tests in mice.

PHARMACOKINETIC STUDIES

The purpose of the pharmacokinetic evaluations was to confirm the hypothesis that glycocholic acid-lecithin mixed micelles rapidly dissociate following the intravenous injection. The sponsor expects that the separated components then behave like the phospholipid and bile acid present endogenously. Since both components bind to plasma proteins, an in vitro investigation of the interaction potential of the solubilizer with plasma protein binding of various representative drugs was determined.

EFFECT OF MIXED MICELLES FORMULATION ON THE PHARMACOKINETICS OF GLYCOCHOLIC ACID IN DOGS (REF. III G1)

Radiolabeled glycocholic acid was administered I.V. either as a mixed micelle preparation or as aqueous solution. These were compared in a cross-over study in two dogs. Plasma concentration vs time curves were very similar. Differences began to appear when glycocholic acid plasma concentration decreased to approximately 1.5% of the starting values. The terminal half-life of glycocholic acid was slightly longer than with the aqueous solution while the volume of distribution of glycocholic acid did not differ between the two formulations. The longer half-life appeared to be the result of the lower total plasma clearance. This difference occurred at levels within the physiological range and not considered to be relevant to the patient population.

INTERACTION OF MIXED MICELLES WITH THE PROTEIN BINDING OF VARIOUS DRUGS (REF. III G2)

The protein binding of various drugs known to bind to different sites on plasma proteins were tested to determine effects of mixed micelles on the binding of these drugs. The following drugs were tested

Binding to albumin:

Diazepam, warfarin, ketoprofen, furosemide, probenecid, prazosin, quinidine, propranolol

Binding to α 1-acid glycoprotein or other proteins:

Disopyramide, prednisolone

Concentrations of mixed micelles corresponding to the maximum possible plasma concentrations achieved following intravenous injection of the highest clinical doses had little or no effect on the unbound fraction of the drugs that bind exclusively to albumin. At 5X maximum therapeutic levels of free drug fractions were substantially increased up to 45%. An increase of 50-85% was noted for prazosin, quinidine and propranolol. This was not tested in vivo.

OVERALL SUMMARY AND EVALUATION

Cernivit™-12 IV has been marketed in Europe since 1982. Due to vitamin shortage in the US, Cernivit™-12 IV has been imported for use in the United States since 1996.

The sponsor provided one month toxicology studies in rats and dogs with fresh and degraded micelles mixture. A single one month study in dogs with Cernivit™-12 IV was also provided. Basically, the following was determined:

1. The accelerated degradation product, 17-7465/002 appeared to be more toxic than 17-7465/001, the intact product. Thus, care should be taken to minimize the exposure of this product to extreme storage conditions.