Final Report

Study Title	SPP 100B Aliskiren hemifumarate:14 Day Oral (Gavage in Methylcellulose/Dietary) Administration Study in the Mouse
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Covance Study Number	1940/049
Report Issued	May 2002
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RESULTS

Toxicokinetics (Appendix 2)

Analytical

The calibration and quality control data indicate that the method performed reliably during the study sample analyses (Tables 1 and 2 of Appendix 2).

Plasma Concentrations

SPP 100

Plasma concentrations for individual animals are reported in Table 3 of Appendix 2.

Concentration levels observed for Groups 4M and 4F are comparable for all timepoints and show a similar trend. Likewise concentration levels for Groups 5M and 5F are comparable and also follow a similar trend.

The highest mean observed SPP 100 levels are approximately 10-fold higher in animals from Group 5 than compared those from Group 4. The highest mean levels are observed at 1 hour for Group 4M, 16 hours for Group 4F and 4 hours for both Group 5M and Group 5F animals.

There appears to be a sharp decrease in concentrations observed in group 5 from the 16 hour timepoint although animal 92 from Group 5F has a much higher level of SPP 100 than is observed in other animals from the same group. Levels of Group 4 animals remain constant throughout all timepoints analysed with no decreasing trend evident.

Mortality

Two mice were found dead during the course of the study and one mouse died accidentally. Animal number 25 (Group 5M), was found dead on Day 6. Factors contributory to death were considered to include necrosis and ulceration of the respiratory epithelium of the nasal passages.

Animal number 56 (Group 5F), was found dead on Day 7. Factors contributory to death were considered to include necrosis and ulceration of the respiratory epithelium of the nasal passages.

Animal number 57 (Group 5F) died accidentally on Day 12 during the haematology and clinical chemistry bleed.

No other deaths occurred in any of the other dose groups.

Clinical signs (Appendix 3)

There was no consistent pattern of variation in clinical signs data to suggest any effect of treatment with the test article. On one occasion, immediately after dosing, the males receiving the gavage formulation were observed to have the post dose observation of paddling. This observation was on one occasion in four animals and therefore was difficult to attribute to a treatment related effect. The observations of thinning fur, staining of fur and sores/lesions were within the expected range for animals of this age and strain.

Body weight (Table 1, Appendix 4)

There was no consistent pattern of variation in body weight data to suggest any effect of treatment with the test article.

Food consumption (Table 2, Appendix 5)

For the high dose males and females receiving the test article through diet, the amount of food consumed was reduced when compared to control values. For the high dose females however, this reduced food intake was not the lowest group mean intake in the animals receiving the test article in diet. Due to the short duration of the study, it is therefore difficult to draw any definite conclusions from the food consumption data.

Compound consumption (Table 3)

The compound consumption was variable over the two weeks of study. This variation could be expected with a study of this short duration.

Haematology (Table 4, Appendix 6)

There was no consistent pattern of variation in haematology data to suggest any effect of treatment with the test article.

For the Group 3 males, the group mean values for reticulocytes, absolute reticulcytes and platelet count were elevated when compared to control values. This elevation could

CONCLUSION

The dietary administration of SPP 100 at dose levels of 150, 600 and 1000 was well tolerated over the 14 day period, with no effects on clinical signs, body weight haematology, clinical chemistry or organ weight data. There were possibly slight effects on the food consumption of the high dose males and females receiving the dietary formulation, but no effects for the animals receiving the gavage formulation.

AUC values were approximately 6-times greater for the oral (gavage) animals than for dietary animals.

In two mice found dead there were microscopic findings, consisting of inflammation, necrosis and inflammation in the nasal cavities at 1000 mg/kg/day for the oral (gavage) administration animals. It is therefore considered that oral (gavage) treatment of mice with SPP 100 at 1000 mg/kg/day would be considered too high for any subsequent studies. All dietary dose levels were well tolerated.