2.7.3 SUMMARY OF CLINICAL EFFICACY

2.7.3.1 Background and Overview of Clinical Efficacy

No clinical efficacy studies were conducted by the applicant in support of this hybrid application. The efficacy and safety of spironolactone in adults is supported by RCTs and non-randomised interventional and observational studies. In children, published information on efficacy and safety is limited and largely premised on adult data. A summary of the clinical efficacy data identified in the literature is presented in Table 2.7.3.1.

2.7.3.2 Summary of Results of Individual Studies

2.7.3.2.1 Clinical studies of spironolactone in adults with Heart Failure

Randomised Controlled Trials of Spironolactone in Adults with Heart Failure

Randomised Aldactone Evaluation Study (RALES)

[redacted]

[redacted]

Treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT)

[redacted]

Results from TOPCAT revealed that spironolactone had a beneficial effect in only one of the components of the primary outcome; [redacted]

[redacted]

2.7.3.2.2 Clinical studies of spironolactone in children with heart failure

[redacted]

[redacted]

2.7.3.2.3 Ascites

In a randomized comparative study 40 nonazotemic cirrhotic patients with ascites and avid sodium retention were randomly allocated into two groups. Group 1 contained 21 patients treated with furosemide; group 2 contained 19 patients treated with spironolactone. The initial doses were 80 and 150 mg/day, respectively. These doses were increased to 160 and 300 mg/day, respectively, if there was no response. Cases not responding to furosemide and spironolactone were later treated with spironolactone and furosemide, respectively. In group 1, 11 of the 21 patients responded to furosemide, while in group 2, 18 of the 19 patients responded to spironolactone ($p < 0.01$). Of the 10 patients in group 1 not responding to furosemide, 9 responded later to spironolactone. The diuretic response to furosemide and spironolactone was related to the activity of the renin-aldosterone system. Patients with higher renin and aldosterone did not respond to furosemide and required 300 mg/day of spironolactone to achieve a diuretic response. These results indicate that (a) at the dosages used in the study, spironolactone is more effective than furosemide in nonazotemic cirrhosis with ascites, and (b) the activity of the renin-aldosterone system influences the diuretic response to furosemide and spironolactone in these patients [redacted]

2.7.3.2.4 Nephrotic Syndrome

[redacted] evaluated the treatment of severe oedema in NS with diuretics alone. Thirty children with NS and severe oedema were enrolled in a prospective study in two phases. The difference between the two phases was the criteria used for differentiating VE and VC patients.

[redacted]

[redacted]

[redacted] he authors concluded that FeNa is useful in distinguishing VC versus VE in NS children with severe oedema. The use of diuretics alone in VE patients is safe and effective [redacted].

2.7.3.2.5 Primary Hyperaldosteronism

In a randomized double-blind trial that compared the efficacy, safety and tolerability of eplerenone to that of spironolactone (100–300 vs.75–225 mg, respectively) in patients with PA, it was found that spironolactone was superior to eplerenone for blood pressure lowering and associated with higher rates of male gynaecomastia (21% vs.5%) and female mastodynia (21% vs. 0%) [redacted]

A prospective study compared 54 patients with primary hyperaldosteronism who had treatment with either spironolactone or surgical resection of an adrenal adenoma (Catena et al 2008). The control group (n=108) was patients with primary HT matched for age, gender, BMI, and duration of HT. The study found that before treatment, patients with primary hyperaldosteronism had a greater prevalence of cardiovascular events than those with primary HT. After treatment of the mineralocorticoid excess whether it be by surgical resection of adenomas or by spironolactone; there was no longer an elevated cardiovascular risk for those with primary hyperaldosteronism. Patients were prospectively followed up for a mean of 7.4 years after adrenalectomy or treatment with spironolactone, with a combined end point including myocardial infarction, stroke, any type of revascularization procedure, and sustained arrhythmias. During follow-up, blood pressure was comparable in the PA and primary hypertension group, and 10 patients in the PA group and 19 in the primary hypertension group reached the end point (P = 0.85). Cox analysis showed that age <52 years and a history of hypertension lasting <10 years were associated with a better cardiovascular outcome in PA. Actuarial analysis of patients treated with adrenalectomy vs. spironolactone did not reveal significant difference in the occurrence of the combined end point (HR, 1.26; 95% CI, 0.36–4.44; P = 0.71).

The long-term outcomes of renal function after treatment of PA were investigated in the same cohort, by measuring the rates of change of glomerular filtration rate and albuminuria.71 After the initial fall in creatinine clearance, due to correction of the aldosterone-induced intrarenal hemodynamic adaptation, subsequent declines of glomerular filtration in patients with PA (−1.15ml/min/1.73m2/year) and primary hypertension (−1.06ml/min/1.73m^2/year) were comparable (P = 0.49). Urinary albumin losses did not differ between patients with PA and primary hypertension during the long-term phase of follow-up (P = 0.56). Analysis of renal outcomes in

patients with PA who were treated with adrenalectomy or spironolactone did not reveal significant difference (P = 0.87).

[redacted]

One clinical trial investigated the therapeutic effect of Spironolactone in 35 infants between 1 week and 10 months old. 4/15 participants in the study group (n=15) received spironolactone (1-3 mg/kg/24 h. The control group (n=20) received no treatment. No specific benefit or adverse effect was stated. This study reported that the 4 patients receiving Spironolactone showed improved diuresis and decreased serum aldosterone. Due to the nature of the study and the small sample size, it is not possible to make a definite recommendation [redacted]

2.7.3.3 Comparison and Analyses of Results Across Studies

[redacted]

2.7.3.4 Appendix

Not applicable.