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Table 25-1 List of Abbreviations and Definition of Terms

Abbreviation	Definition
6 β -OH-7 α -TMS	6- beta-hydroxy-7 α -thiomethylspironolactone
7 α -TMS	7-alpha-(thiomethyl) spironolactone
λ_z	Terminal rate constant
ACE	Angiotensin Converting Enzyme
ANOVA	Analysis of Variance
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
GCP	Good Clinical Practice
H+	Hydrogen
HERG	Human ether-a-go-go-related gene
HPLC	High Performance Liquid Chromatography
ICH	International Committee for Harmonisation
K+	Potassium
LC-APCI-MS	Liquid Chromatography-Atmospheric Pressure Chemical Ionization-Mass Spectrometry
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
max	Maximum
MCTs	Medium Chain Triglycerides
MHRA	Medicines & Healthcare products Regulatory Agency
min	Minimum
mmHG	Millimetres of mercury
MRA	Mineralocorticoid Receptor Antagonist
n	Number of subjects
Na+	Sodium
NICE	National Institute for Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
PAR	Public Assessment Report
PIL	Product Information Leaflet
PL	Product Licence
RALES	Randomised ALdactone Evaluation Study
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	Elimination half-life
T _{max}	Time to maximum plasma concentration
UK	United Kingdom

2.5.1 PRODUCT DEVELOPMENT RATIONALE

This is a UK National Marketing Authorisation Regulation 52 hybrid application (previously Article 10(3) of Directive 2001/83/EC) for a new oral solution containing the established active substance, spironolactone, described in European and British Pharmacopeial monographs.

Two strengths of the new oral solution have been developed by Rosemont Pharmaceuticals Limited:

Spironolactone 50mg/5mL

Spironolactone 25mg/5mL

These products are non-aqueous solutions developed to offer an alternative pharmaceutical form to those patients who may have difficulty swallowing, or require a lower titrated dose, particularly relevant for elderly and paediatric patients. An aqueous spironolactone suspension has been manufactured and sold by Rosemont Pharmaceuticals Limited as a “Specials” product for more than 30 years indicating the clinical need for a spironolactone solution product. Commercialisation of this “Specials” formulation is not feasible as the aqueous product could not be formulated to have a sufficient shelf-life hence the development of the non-aqueous solution.

The spironolactone non-aqueous solution products have been developed as new formulations equivalent to an existing marketed product, Aldactone Film-Coated Tablets, with equivalent indications and posology proposed.

2.5.1.1 Pharmacological Class and Properties of the Medicinal Product

Spironolactone is a mineralocorticoid receptor antagonist (MRA), the first to be developed and acts as a competitive aldosterone antagonist. It increases sodium excretion whilst sparing potassium loss at the distal renal tubule and therefore belongs to the Pharmacotherapeutic group – Diuretic; potassium sparing; aldosterone antagonists; ATC code C03DA01.

Spironolactone was developed in the 1950s and has several structural elements in common with progesterone (Struthers et al., 2008). It was the first diuretic developed to specifically inhibit a particular renal transport process involved in handling sodium (Sica, 2005). Due to its similarity to progesterone, at high doses spironolactone exhibits anti-androgenic activity which manifest as painful gynaecomastia and other sexual adverse effects (Lainscak et al., 2015).

Spironolactone has been extensively used in clinical practice over the last 60 years and remains widely used today (Yang & Young, 2016). It is included on the World Health Organisation (WHO) Model List of Essential Medicines (WHO, 2019). It has an established therapeutic use and safety profile determined by its pharmacological action which has been further elucidated over recent years with the developments in molecular pharmacology (Kolkhof & Borden, 2012). Therapeutic indications relate to spironolactone’s inhibition of aldosterone effects. With further mechanisms revealed on the role aldosterone has in the pathophysiology of cardiovascular and renal disease, the effects of spironolactone are now understood to extend beyond that of diuresis (Bauersachs et al., 2015). The addition of spironolactone to standard therapy in patients with severe heart failure has been shown to reduce both morbidity and mortality (Pitt et al., 1999). Patients with primary aldosteronism have an increased risk of cardiovascular morbidity and mortality therefore early diagnosis and treatment is vital with spironolactone playing a key role. Spironolactone is considered the primary MRA for patients with primary aldosteronism due to bilateral adrenal disease (Funder et al., 2016).

Spironolactone also has antihypertensive effects and is often used as a supplementary therapy for the treatment of hypertension however this is an unlicensed indication for the majority of spironolactone products in the UK.

Due to its anti-androgenic effects spironolactone has also gained an off-label use in dermatology (Searle et al., 2020).

2.5.1.2 Target Indications and Posology

The target indications are consistent with those as they appear on the Aldactone tablet Summary of Product Characteristics (SmPC), namely:

- congestive cardiac failure
- hepatic cirrhosis with ascites and oedema
- malignant ascites
- nephrotic syndrome
- diagnosis and treatment of primary aldosteronism

Posology for these indications is summarised in Table 25-2.

Table 25-2 Overview of Indications and Posology for Spironolactone Solution

Indication	Initial Daily Dose of Spironolactone	Maintenance Dose
Congestive Heart Failure with oedema	100 mg – once or in divided doses Range 25 to 200 mg	Individually determined
Severe Heart Failure	In conjunction with standard therapy if serum K ⁺ ≤ 5.0 mEq/L and creatinine ≤ 2.5 mg/dL: 25 mg	Dose can be increased to 50 mg as clinically indicated If 25 mg once daily is not tolerated, dosing interval can be reduced to every other day
Hepatic cirrhosis with ascites and oedema	If urinary Na ⁺ /K ⁺ ratio > 1.0: 100 mg If urinary Na ⁺ /K ⁺ ratio < 1.0: 200 to 400 mg	Individually determined
Malignant Ascites	100 to 200 mg In severe cases doses may be gradually increased up to 400 mg/day	Individually determined
Nephrotic syndrome	100 to 200 mg Only advised if glucocorticoids are insufficient	
Primary aldosteronism ¹	100 to 400 mg in preparation for surgery	For those not suitable for surgery the lowest effective dose should be individually determined

¹Use of spironolactone in the diagnosis of primary aldosteronism is described in the SmPC

The spironolactone oral solution is particularly recommended for children and adults with swallowing difficulties, as it allows for a secure and precise dose. Only the provided dosing syringe should be used as the products are incompatible with polystyrene or PVC, this information is included on the proposed product information (Section 6.2 of the SmPC and Section 3 of the Product Information Leaflet (PIL)).

Paediatrics should only be treated under the guidance of a paediatric specialist. An initial daily dosage should provide 1-3 mg of spironolactone per kg body weight in divided doses. Dosage should be adjusted on the basis of tolerability and effectiveness.

2.5.1.3 Brief Description of Clinical Development Programme

In accordance with Regulation 52 hybrid applications no new clinical efficacy and safety studies have been completed. This application is largely based on bibliography supported by pharmacokinetic data from a bioequivalence study () involving the higher strength (50mg/5mL) non-aqueous solution. A biowaiver is included for the lower strength (25mg/5mL) product.

The bioequivalence study, () was an open-label, fed, single dose, two treatment, two period, crossover study of spironolactone oral solution 50mg/5mL (10 mL) and Aldactone 100 mg film-coated tablets in normal, healthy, adult volunteers conducted (). Spironolactone concentrations in plasma were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The study was conducted in accordance with The International Council for Harmonisation Guideline for Good Clinical Practice (ICH GCP E6 (R2) 2016), the Declaration of Helsinki (Brazil, 2013), European Medicines Agency (EMA, 2010) guidelines for bioequivalence studies and the regulatory requirements of India.

() This has now been removed from the final formulation as it is no longer available. This minor formulation change is not anticipated to have any significant effect on the physiochemical or biological properties of the drug product, nor the solubility of the active substance in the solution. This is evidenced by the results from comparative investigations presented in Module 3.2.P.2 and summarised in the Quality Overall Summary.

Results from () demonstrated equivalent systemic exposure between the 50mg/5mL spironolactone solution (test) and the 100 mg Aldactone film-coated tablet (reference product) but with different rates of absorption; the spironolactone solution was absorbed more slowly. Argumentation is presented in Section 2.5.2.2 to justify why this difference in the rate of absorption is not relevant to the clinical uses of spironolactone supporting the position that this study is suitable to support applications for the two liquid formulations with no additional data.

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()

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Spironolactone ($C_{24}H_{32}O_4S$) is a white to light tan powder with a slightly bitter taste. It is usually odourless or has a slight smell of thioacetic acid (Dollery, 1991). It is poorly soluble in water. Spironolactone oral preparations, mainly tablets, are available in 12.5 mg to 100 mg strengths. Combination oral preparations are also available with other diuretics such as frusemide and hydroflumethiazide.

An aqueous spironolactone suspension has been manufactured and sold by Rosemont Pharmaceuticals Limited as a “Specials” product for more than 30 years. Due to the formation of hydrated spironolactone crystals after storage beyond 1 year, the formulation was re-developed as a non-aqueous solution.

2.5.2.1 Overview of Formulation

The proposed formulation is a clear colourless to pale yellow non-aqueous solution of spironolactone dissolved in medium chain triglycerides (Miglyol™) flavoured with peppermint oil. Medium chain triglycerides (MCTs) liquid was chosen as the solubilising agent as it has previously been successfully used by Rosemont Pharmaceuticals as a carrier solvent for licensed clonazepam solutions (PL 00427/0157-8) and an [REDACTED]

The oral solution will be supplied with a 10 mL oral dosing pipette. This device has been demonstrated to be suitable for the medicinal product, and its graduations for the intended population have been taken into account. The accuracy at minimal dose (0.5 mL) has been proven. The graduated scale on the syringe corresponds with the SmPC dosing advice and is suitable for the dosing range for children per kg body weight (Module 3.2.P.2.4.)

[REDACTED] Studies show that no signs of drug substance degradation are evident in samples prepared under high temperatures and stored at 50°C (Module 3.2.P.2.1.2).

The formulation and manufacturing process has been developed to ensure the water activity values for the product fall below 0.6 indicating that microbial growth cannot be supported. Therefore a traditional preservative is not required.

Table 25-3 Overview of Development and Final Formulations

Ingredient	Development Formulation ¹		Final Formulation		Function	Quality Standard
	25mg/5mL	50mg/5mL	25mg/5mL	50mg/5mL		
Spirolactone (mg)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Active Ingredient	Ph.Eur.
Advantame (mg)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Sweetener	HSE
Peppermint oil (mg)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Flavour	
Medium Chain Triglycerides	[REDACTED]				Solvent	Ph.Eur.

¹50mg/5mL strength used in bioequivalence study [REDACTED]

Abbreviations: HSE = Health, Safety & Environment; Ph. Eur = European Pharmacopoeia

2.5.2.2 Overview of Biorelevant in vitro or Bioavailability data

In-vitro dissolution data has been generated for the 50mg/5mL proposed oral solutions (non-aqueous formulation, biostudy batch) compared with Aldactone 100 mg tablets (reference product) at pH 1.2, 4.5, & 6.8 (Module 3.2.P.2.2.4). The oral solution, as used in the biostudy,

undergoes much quicker dissolution over the first 20 minutes than the reference tablet. This is attributed to the tablet going through disintegration before the active substance can be released into the solution. From 30 minutes onwards the profiles are much more comparable.

Removal of the Advantame from the final formulation has not altered the dissolution profile as demonstrated by the comparative dissolution characteristics (Module 2.3.P.2.2.4)

The bioequivalence study, [REDACTED], was an open-label, fed, single dose, two treatment, two period, crossover study of spironolactone oral solution 50mg/5mL (10 mL equivalent to 100 mg spironolactone) and Aldactone 100 mg film-coated tablets in normal, healthy, adult volunteers conducted by [REDACTED]

[REDACTED] (including bioanalysis). Potential participants were screened 28 days prior to dosing in Period 1. During each period randomised treatment was administered with 240 mL of water 30 minutes after serving breakfast and blood samples for bioanalysis collected pre-dose and at 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 12.00, 24.00 and 36.00 hours post-dosing. Participants remained in the unit for 12 hours post-dosing and there was a wash-out period of 9 days between treatments. The plasma samples were analysed for spironolactone concentrations using a validated LC-MS/MS method developed by the bioanalytical department at [REDACTED] calibration range 0.744 to 303.27 ng/mL). Pharmacokinetic parameters were derived for each subject using the non-compartmental model of Phoenix WinNonlin™ (version 8.1). Descriptive statistics were reported and the 1n-transformed pharmacokinetic parameters, C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ for spironolactone analysed using an analysis of variance (ANOVA) performed using PROC GLM of SAS™ (version 9.4). The sample size calculation required 34 participants to complete the study and was based on assuming a test/reference ratio of 90 – 110 with an intra-subject variability of 28%. The study was conducted in accordance with ICH GCP (E6 (R2) 2016), the Declaration of Helsinki (Brazil, 2013), EMA guidelines for bioequivalence studies (EMA, 2010) and the regulatory requirements of India.

The design of the study was appropriate. As there is no liquid formulation currently registered in the UK the proprietary tablet formulation - Aldactone 100 mg film-coated tablets (PL00057/0927, Pfizer Healthcare) was considered the applicable reference product. The LC-MS/MS analytical method was sensitive enough to measure spironolactone accurately and precisely and the washout period sufficient to ensure spironolactone concentrations were below the limit of quantification for all subjects prior to the second dosing period. A LC-MS/MS method for spironolactone analysis has previously been described in the literature and applied to a bioequivalence study (Vlase et al., 2011). Dosing of spironolactone is recommended with food (Aldactone SmPC) therefore in accordance with bioequivalence guidelines a high fat/high calorie breakfast (vegetarian) was provided to study participants prior to dosing. As the SmPC does not contain any specific instruction with respect to spironolactone administration and food, food was provided 30 minutes prior to dosing and consumed within this time period. The sampling intervals were appropriate to assess pharmacokinetic parameters with the number of completed subjects just exceeding the required sample size although the intra-subject variability observed in the study was higher (30.7%) than that assumed (28%). Assessment of bioequivalence of spironolactone formulations has altered over the years as more information concerning relative proportions of parent drug and active metabolites has come to light. With the sensitivity of analytical assays improved, a single dose bioequivalence assessment of the parent drug is in accordance with the EMA bioequivalence guideline (EMA, 2010).

Overall 44 participants (all male) were recruited of which 43 were dosed and 37 completed and were included in the pharmacokinetic analysis. Baseline characteristics did not differ between

the study population overall and those included in the bioequivalence evaluation. For the bioequivalence population the mean (SD) age and BMI were 31.7 (6.96) years and 22.56 (3.345), respectively. Descriptive statistics for all pharmacokinetic parameters calculated are provided in Table 25-4 with the statistical analysis of bioequivalence provided in Table 24-5. Figure 25-1 provides a pictorial representation of the mean plasma spironolactone concentration and time curves for the test and reference products.

Table 25-4 Descriptive Statistics for Spironolactone Pharmacokinetic Parameters from [REDACTED] (n=37)

100 mg Spironolactone Product	Arithmetic Mean (SD) Pharmacokinetic Parameter						Median (min-max)
	C _{max} (ng/mL)	AUC _(0-t) (ng.h/mL)	AUC _(0-inf) (ng.h/mL)	t _{1/2} (h)	λ _z (1/h)	AUC_% Extrapol_obs (%)	T _{max} (h)
Test ¹	118.11 (49.242)	387.98 (142.344)	395.85 (143.608)	3.51 (1.770)	0.265 (0.1466)	2.14 (1.092)	4.66 (1.33-5.52)
Reference ²	145.75 (64.474)	356.32 (125.197)	363.71 (126.363)	3.43 (1.945)	0.255 (0.1079)	2.14 (0.769)	1.66 (1.33-4.00)

¹Spironolactone 50mg/5mL oral solution – 10 mL (Rosemont Pharmaceuticals Limited)

²Aldactone 100 mg film-coated tablet (Pfizer Limited manufactured by [REDACTED])

Abbreviations: λ_z = terminal rate constant; AUC = area under the plasma concentration versus time curve; AUC_Extrap_obs = residual area of AUC at end of study; C_{max} = maximum measured plasma concentration; h = hour; max = maximum; min = minimum; SD = standard deviation; t = time; t_{1/2} = terminal half-life; T_{max} = time to reach maximum plasma concentration

Table 25-5 Spironolactone Bioequivalence Evaluation from [REDACTED] (n=37)

Parameter	Geometric Least Squares Mean		Ratio (T/R)	90% Confidence Interval	Intra-subject CV (%)	Study Power (%)
	Test (T) ¹	Reference (R) ²				
lnC _{max}	107.327	133.291	80.5	71.53 – 90.64	30.7	92.8
lnAUC _(0-t)	360.989	338.339	106.7	100.27 – 113.53	15.9	100.0
lnAUC _(0-inf)	368.955	345.774	106.7	100.36 – 113.45	15.6	100.0

¹Spironolactone 50mg/5mL oral solution – 10 mL (Rosemont Pharmaceuticals Limited)

²Aldactone 100 mg film-coated tablet (Pfizer Limited manufactured by [REDACTED])

Abbreviations: AUC = area under the plasma concentration versus time curve; C_{max} = maximum measured plasma concentration; CV = coefficient of variation; R = reference; T = Test

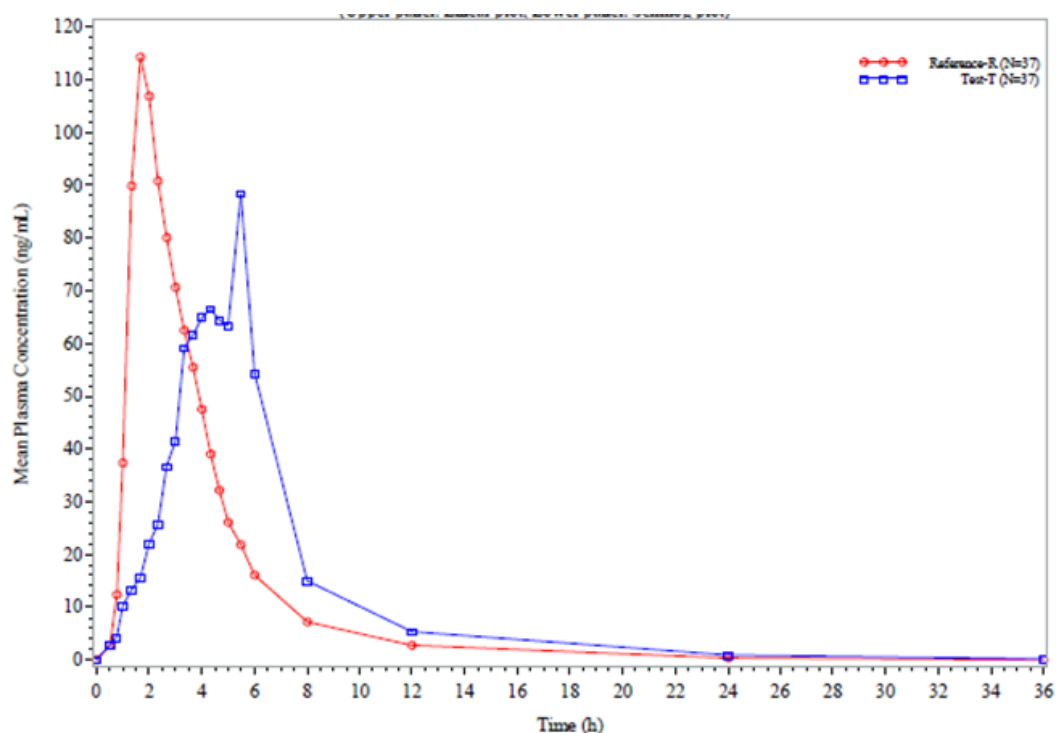


Figure 25-1 Mean Plasma Concentration versus Time Curves for Spironolactone Solution and Aldactone from [REDACTED]

The AUC data from [REDACTED] demonstrated the systemic exposure in healthy male subjects was equivalent between the 10 mL/100 mg dose of the 50mg/5mL spironolactone solution (test) and the 100 mg Aldactone film-coated tablet (reference product). However, the rate of absorption differed between the two formulations as demonstrated by the lower C_{max} and longer T_{max} (median T_{max} 4.66 hours and 1.66 hours for test and reference formulations, respectively). The rate of elimination was the same with no difference noted in the terminal half-life (mean $t_{1/2}$ 3.51 hours and 3.43 hours for the test and reference, respectively).

A different rate of absorption could be expected where two differently formulated products are compared as in this case (tablet vs. oral oil solution). Perhaps based on the dissolution data and the fact the spironolactone was already in solution it may have been expected that the rate of absorption of the spironolactone non-aqueous solution would have been faster than the tablet. However, the dissolution testing did not use bio-relevant media and therefore had limited value in predicting *in vivo* performance on the non-aqueous solution compared with the tablet formulation (Baxevanis et al., 2016).

The observed difference in absorption rate is attributed to the MCT solution of spironolactone. In general the inclusion of a high fat meal in a bioequivalence study is considered a worst-case scenario with respect to the effect of food on absorption due to the delay in gastric emptying caused by the fat content of the meal (EMA, 2012). With spironolactone tablets food enhances absorption compared to the fasting state possibly because first-pass metabolism is reduced (Overdiek & Merkus, 1986). It has been shown that liquid fat can separate from the solid food component and float above the aqueous phase in the fundus of the stomach and empty last. Further the order of ingestion of different meal components can influence gastric emptying and the intra-gastric distribution of fat (Marciani et al., 2007). In the bioequivalence study the treatments were administered after ingestion of a high fat meal. It is therefore likely that the MCT liquid formulation was not as evenly distributed as the tablet formulation through the

gastric contents with a significant proportion sitting above the aqueous phase and therefore took much longer to empty into the small intestine and reach the sites of absorption.

From Figure 25-1 the mean plasma spironolactone concentration-time curve from the spironolactone non-aqueous solution was not as smooth as that from the tablet, there appears to be a second C_{\max} peak. However, examination of the individual time point data indicates this is due to the more variable absorption from the spironolactone solution probably due to the differences in gastric motility and gastric emptying that impacts the spironolactone solution more than the tablet.

Oral absorption of spironolactone is known to be highly variable due to its low aqueous solubility (Dollery, 1991) and values for pharmacokinetic parameters vary across studies (see Table 25-6). However, the values observed for the pharmacokinetic parameters for both spironolactone products in [REDACTED] are consistent with the more recent bioequivalence studies included in recent public assessment reports (PARs). Mean spironolactone plasma levels fell below the lower limit of quantification after 12 hours for the spironolactone solution and reference product, this is longer than previously published but may be due to the improved sensitivity of the bioanalytical assay. Mean half-life data varied across the studies summarised in Table 25-6 from 1.4 hours (Gardiner et al., 1989) to 4.5 hours (PAR NL/H/3508/001-003/MR). In the present bioequivalence study the mean half-life data for both reference and test products fell between these values (3.43 and 3.51 hours, respectively).

Table 25-6 Variability of Published Pharmacokinetic Parameters following a single 100 mg dose of Spironolactone

Reference	Population	Product (100 mg)	C_{\max} (ng/mL)	$AUC_{(0-t)}$ (ng.h/mL)	$AUC_{(0-inf)}$ (ng.h/mL)	$t_{1/2}$ (h)	T_{\max} (h)	Method
PAR PL12762/0544-0547 Study C [REDACTED]	Male, n=unk. Fed	Test tablet	136.89 ¹	358.60 ¹	369.99 ¹	-	-	Unk.
		Reference	135.25 ¹	344.57 ¹	355.67 ¹	-	-	
PAR NL/H/3508/001-003/MR	Male, n=59 Fed	Test tablet	116 (55)	288 (103)	300 (110)	4.5 (1.8)	2.0 ²	Unk.
		Reference	119 (67)	288 (128)	299 (134)	4.5 (1.6)	2.0 ²	
Xu et al., 2008	Male, Chinese, n=20 Fasting	Test tablet	48.34 (21.16)	148.35 (39.5)	154.17 (40.65)	2.36 (0.32)	1.4 (1.0)	LC-APCI-MS ³
		Reference	47.40 (23.40)	144.39 (53.02)	150.41 (56.03)	2.37 (0.32)	1.0 (0.6)	
Gardiner et al., 1989 Day 1	Male, n=12 Fed ⁴	Reference	72 (45)	177 (86)	-	1.4 (0.5)	2.8 (1.3)	Modified HPLC

¹Geometric least square means, values rounded up to 2 decimal places

²Median values

³Simultaneous determination of spironolactone and active metabolite canrenone

⁴Light breakfast

Reference Product was Aldactone 100 mg tablet in all cases

Abbreviations: HPLC = high-pressure liquid-chromatography; LC-APCI-MS = liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry; PAR = public assessment report; PL = product

licence; unk. = unknown

As there is no direct correlation with spironolactone plasma levels and clinical effect the difference in the rate of absorption observed in the bioequivalence study becomes clinically less important, particularly when the pharmacological action and clinical use of spironolactone is taken into account.

The onset of action of spironolactone is slow, with a peak clinical response occurring more than 48 hours after the first dose (Sica, 2005). This is partly thought to be due to the time taken for the active metabolites of spironolactone to reach steady state. Spironolactone is rapidly metabolised to three active metabolites with longer half-lives (13.8-16.5 hours) than the parent drug (Gardiner et al., 1989).

Drug treatment with spironolactone starts at the lowest dose, with monitoring and titration upwards depending on tolerability and treatment effect. The principal is to avoid hyperkalaemic effects. There is a correlation between the hyperkalaemic effect of spironolactone concentrations (and its metabolites), with 8% increase in hyperkalaemia with a doubling of the dose from 25mg to 50mg and 50mg to 100mg of spironolactone (Sica, 2005). The oral solution and oral dosing syringe permit suitable lower doses to be given to the patient with dosing accuracy to 5 mg.

The lack of equivalence or a lower C_{max} value, where systemic exposure (AUC data) to spironolactone remains the same between reference and test product would not prevent safe and effective use in a clinical setting. The lower C_{max} values are considered to not be clinically significant, as to achieve a clinical effect, the drug requires several days to reach steady state plasma levels for its pharmacologically more active metabolites.

Therefore the AUC (the amount of drug in the body) is of greater importance than C_{max} to determine therapeutic equivalence for spironolactone. In [REDACTED] the AUCs were bioequivalent, thereby demonstrating clinical equivalence for spironolactone. Spironolactone absorbed systemically, either via the solid dose format or the oil based MCT solution, is distributed, metabolised and eliminated in the same manner, so systemic exposure for the metabolites can be considered to be the same at steady state for both the MCT oil solution and the solid dose product.

Schütz et al., (1991) showed that bioequivalence for a spironolactone/furosemide combination is more conclusively verified on the basis of pharmacodynamic parameters (urine production and electrolyte excretion) than on the basis of pharmacokinetic parameters. These considerations are applicable in particular, *“to drugs displaying large inter-individual variations in serum levels and/or a poor correlation between serum levels and effect.”*

Spironolactone should be titrated according to both symptoms and adverse effects. This standard approach to therapy also minimises any clinical effect of small changes in the pharmacokinetic profiles of different formulations, supporting the position of the applicant that this study is suitable to support applications for the two liquid formulations with no additional data.

Biowaiver

A biowaiver is requested for the lower strength product (25mg/5mL). Data from *in vitro* dissolution testing show drug release characteristics for the two strengths were highly similar (Module 3.2.P.2.2.4) supporting the relevance of the bioequivalence results for the 50mg/5mL spironolactone solution to the lower strength. Both of the proposed spironolactone oral solutions are manufactured by the same manufacturing process, on the same manufacturing site

and have the same qualitative formulae. Although the composition of the two strengths are not quantitatively proportional the amount of spironolactone is less than 5% of the product's weight and the amount of MCTs is only changed to account for the change in the amount of spironolactone.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Spirolactone is a potent, non-selective, competitive antagonist at the mineralocorticoid receptor and blocks the effects of aldosterone. Despite extensive efforts a more selective and equally potent steroidal MRA is yet to be developed (Kolkhof & Borden, 2012). Spirolactone also acts at the androgen receptor and progesterone receptor which account for spironolactone's characteristic anti-androgenic effects.

2.5.3.1 Pharmacokinetics

Spirolactone is well absorbed after oral dosing with an approximate 70% bioavailability which is increased to approximately 95% if taken with food (Karim, 1978; Overdiek & Merkus 1986). This increase in bioavailability after a meal has led to the recommendation that spironolactone should be administered with food (Melander et al., 1977; Aldactone SmPC). Absorption is variable due its low aqueous solubility but is enhanced by micronisation of the drug (Dollery, 1991). Spirolactone undergoes extensive first-pass metabolism, undergoes enterohepatic recirculation and is extensively bound to plasma proteins. It has been suggested that the increased absorption of spironolactone after food may be attributed to a decrease in the first pass metabolism of spironolactone (Overdiek & Merkus, 1986). Elimination is primarily by the liver.

The metabolism of spironolactone is complex. Two main pathways have been identified leading to sulfur-free or sulfur-containing metabolites (Overdiek & Merkus, 1987). Three active metabolites have been identified:

- 7- α -(thiomethyl) spironolactone (7 α -TMS),
- 6- β -hydroxy-7 α -thiomethylspironolactone (6 β -OH-7 α -TMS),
- Canrenone (7 α -desthioacetyl- δ 6-spironolactone).

The literature cites variable values for the pharmacokinetic parameters of the active metabolites. Some of this variance can be attributed to the different analytical methods employed. In the early stages of spironolactone's therapeutic use the canrenone (7 α -desthioacetyl- δ 6-spironolactone) metabolite was considered the major metabolite based on a non-specific fluorimetric method. Development of a specific high performance liquid chromatography (HPLC) method demonstrated that this fluorimetric method overestimated true canrenone levels and that the sulfur-containing metabolite 7- α -(thiomethyl) spironolactone (7 α -TMS) is the major metabolite following single and repeated doses contributing about 80% of the potassium sparing effect of spironolactone (Gardiner et al., 1989). The food effect is more pronounced for the parent drug than the active metabolites (Overdiek & Merkus, 1986).

Metabolite pharmacokinetic parameters from the literature are summarised in Table 25-7 following a single dose of 100 mg of spironolactone and in Table 25-8 at steady state following once daily dosing with 100 mg spironolactone. The time taken for spironolactone and its active metabolites to reach steady state may account for the delay in the onset of action of spironolactone (Sica, 2005).

Observed steady state C_{max} values for spironolactone have reported to range from 17.0 to 128 ng/mL with less intra-subject variability than that observed after a single dose (Vergin et al., 1997).

Table 25-7 Published Single Dose Pharmacokinetic Parameters for Spironolactone Metabolites from Reference Products following a 100 mg Dose

Study	Metabolite	N	Analytical Method	Pharmacokinetic Parameter				
				C _{max} (ng/mL)	AUC _(0-t) (ng.h/mL)	AUC _(0-inf) (ng.h/mL)	t _½ (h)	T _{max} (h)
Li et al., 2016 ¹	Canrenone (fasting)	20	HPLC-MS/MS	72.4 (29.4)	1478.5 (374.9)	1828.5 (461.6)	23.3 (11.8)	4.6 (2.7)
	Canrenone (fed)	20		110.7 (28.8)	1854.9 (315.1)	2035.0 (345.3)	16.1 (6.3)	4.4 (1.0)
Xu et al., 2008 ²	Canrenone (fasting)	20	LC-APCI-MS	123.35 (27.29)	1911.28 (355.60)	2001.92 (363.78)	13.35 (1.88)	3.4 (1.0)
Schütz et al., 1991 ³	Canrenone (fasting)	12	HPLC	135.8 (13.1)	-	2378 (288)	-	4.2 (0.3)
Gardiner et al., 1989 ¹	7α-TMS	12	Modified HPLC	359 (106)	2242 (477)	-	13.8 (6.4)	3.3 (1.2)
	Canrenone			155 (43)	1546 (323)	-	16.5 (6.3)	4.7 (1.7)
	6β-OH-7α-TMS			101 (26)	1151 (233)	-	15.0 (4.0)	5.4 (1.4)

¹Aldactone reference product

²Source of reference product unclear

³Reference product was Osyrol 100-Lasix (Hoechst AG) – 100 mg spironolactone/ 20 mg furosemide combination tablet

Abbreviations: HPLC = high-pressure liquid-chromatography; LC-APCI-MS = liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry; N = number of subjects (all male)

Table 25-8 Published Steady State Spironolactone Pharmacokinetic Parameters following repeat dosing with 100 mg tablet once daily

Study	Metabolite	N	Analytical Method	Pharmacokinetic Parameter			
				C _{max} (ng/mL)	AUC _(0-t) (ng.h/mL)	t _½ (h)	T _{max} (h)
Vergin et al., 1997 Day 5 Fasting	7α-TMS	24	HPLC	335.1 (108.2)	2333.7 (771.1)	3.4 (0.5) 16.0 (5.9) ¹	2.3 (0.8)
	Canrenone			154.7 (31.4)	2028.8 (323.10)	9.5 (2.7) 23.0 (8.2) ²	3.2 (0.7)
Gardiner et al., 1989 Day 8	7α-TMS	12	Modified HPLC	408 (122)	2557 (568)	13.8 (6.4)	3.2 (1.5)
	Canrenone			202 (44)	2251 (291)	16.5 (6.3)	3.9 (1.6)
	6β-OH-7α-TMS			125 (23)	1586 (269)	15.0 (4.0)	4.2 (1.4)

All male subjects

Aldactone tablets were used in all studies

¹Plasma concentration time profiles had a pronounced biphasic appearance so half-lives for both phases calculated; n=23 for t_{½B}

²Plasma concentration time profiles had a pronounced biphasic appearance so half-lives for both phases calculated; n=20 for t_{½B}

In cirrhotic patients with ascites metabolism of spironolactone is impaired with terminal half-lives of spironolactone and its active metabolites increased. From a study in 9 patients with cirrhosis and ascites reported half-lives were 9.04 hours, 23.9 hours, 57.8 hours and 126 hours for spironolactone, 7 α -TMS, canrenone and 6 β -OH-7 α -TMS, respectively (Sungaila et al., 1992).

2.5.3.2 Pharmacodynamics

Spironolactone passively blocks the physiological and pathophysiological effects of aldosterone. Aldosterone is a mineralocorticoid hormone that promotes:

- the retention of sodium
- the loss of magnesium and potassium,
- sympathetic activation,
- parasympathetic inactivation,
- myocardial and vascular fibrosis,
- baroreceptor dysfunction,
- vascular damage and impairs arterial compliance (Pitt et al., 1999)

In more recent years the role of aldosterone in the pathophysiology of cardiovascular and renal disease has grown with the deleterious effects mostly independent of the systemic effects on blood pressure (Bauersachs et al., 2015). The mechanisms of these effects are both epithelial and non-epithelial (Sica, 2005). The primary epithelial site is the renal tubules but other sites include the salivary glands and gastrointestinal tract. The epithelial effects are mediated via the binding of aldosterone to the Type 1 glucocorticoid receptor, interaction of the ligand-receptor complex with DNA and an adjustment in gene expression. Non-epithelial effects are thought to be mediated by a second messenger system which involves activation of the Na⁺/H⁺ transporter.

Therefore the pharmacodynamics properties of spironolactone include effects on epithelial ion transport and on a spectrum of non-epithelial cellular processes (Sica, 2005), these are summarised in Table 25-9.

Table 25-9 Overview of the Pharmacodynamic Effects of Spironolactone

Pharmacodynamic Mechanism	Effect of Spironolactone
Mineralocorticoid receptor (MR) stability	Destabilises helix; does not promote aldosterone-induced MR degradation
Aldosterone-induced intra-nuclear translocation of MR	Permits nuclear localisation but delayed
Coactivator recruitment	Reduced due to helix, 12 destabilisation SRC-1 recruitment intact but not RNA polymerase II
Epithelial ion transport	Increase urinary Na ⁺ /K ⁺ ratio
Renin-angiotensin axis	Increases renin release and aldosterone levels by disrupting feedback loop
Blood pressure regulation	Little additional effect above 100 mg/day Maximal effect takes 3-4 weeks
Heart failure protection	30% ↓ in all-cause mortality 35% ↓ in hospitalisation for worsening heart failure
Potassium	K ⁺ >5.5 mmol/L in: 13% patients on 25 mg/day 20 patients on 50 mg/day 24% patients on 75 mg/day

Source: Table 3 from Yang & Young; 2016

Therapeutic concentrations of spironolactone block human ether-a-go-go-related gene (hERG) potassium channels which may account for spironolactone's antiarrhythmic effects.

Epithelial Cell Transport of Sodium

Spironolactone is weakly natriuretic but when given to patients with cirrhosis and ascites, particularly in combination with a loop diuretic, a significant natriuretic response can be elicited (Sica, 2005).

Renin-Angiotensin-Axis

Inhibition of the mineralocorticoid receptor in the distal nephron by spironolactone disrupts the renin-angiotensin-aldosterone system causing an increase in renin and aldosterone levels.

Anti-hypertensive Properties

The observed blood pressure effects of spironolactone may be due to both epithelial and non-epithelial actions. Spironolactone destabilises the glucocorticoid receptor and impairs coactivator recruitment (Yang & Young, 2016).

Anti-androgenic Properties

Spironolactone acts as an agonist on the progesterone receptor but is also an androgen receptor antagonist (Rozner et al., 2020) resulting in a decrease in testosterone and an altered testosterone/oestrogen ratio. A deficiency in 5 α -dihydrotestosterone results in feminisation (Searle et al., 2020).

The onset of action for spironolactone is slow, peak responses can occur 48 hours or more after the first dose (Sica, 2005). This is due to spironolactone's complex metabolism and time taken for the active metabolites to reach steady state. However, as the active metabolites have long half-lives once daily dosing is sufficient. The duration of effects on sodium loss and potassium retention can differ though. The potassium sparing effects can persist for several days after discontinuation of spironolactone.

2.5.4 OVERVIEW OF EFFICACY

No additional efficacy studies have been completed with the spironolactone solution as the application is based on the product being a hybrid medicinal product of the reference product (Aldactone) which has been licensed for over 10 years. Bibliographic evidence of the efficacy of spironolactone in the licensed indications as detailed on the SmPC is briefly summarised and discussed in Sections 2.5.4.1 to 2.5.4.5 with other unlicensed indications included in Section 2.5.4.6.

2.5.4.1 Congestive Cardiac Failure

Congestive Cardiac Failure with Oedema

Spironolactone is a useful diuretic in the management of congestive heart failure with oedema. Its mechanism of action helps to limit electrolyte disturbances caused by the oedema and other diuretics when used in combination (Skluth & Gums, 1990). Current NICE guideline NG106 recommends the routine use of diuretics for the relief of congestive symptoms and fluid retention in people with heart failure (NICE, 2018). Dosage should be titrated up and down according to clinical need.

Severe Heart Failure

The efficacy of spironolactone in severe heart failure was shown by Pitt et al. (1999) in the double-blind Randomised Aldactone Evaluation Study (RALES). A total of 1663 patients with severe heart failure (defined as New York Heart Association (NYHA) class IV within 6 months prior to enrolment and in NYHA class III or IV at time of enrolment) from 19 centres in 15 countries were randomised to receive either 25 mg once daily spironolactone (n=822) or matching placebo (n=841) in association with the standard treatment at the time. All patients were being treated with a loop diuretic, 97% with an angiotensin-converting-enzyme (ACE) inhibitor, and 78% with digoxin. Left ventricular ejection fraction was no more than 35%. Patients with a baseline serum creatinine of >2.5 mg/dL (221 µmol/L) or with a baseline serum potassium of >5.0 mmol/L (5.0 mEq/L) were excluded. Patients who tolerated 25 mg spironolactone once daily had their dose increased to 50 mg once daily as clinically indicated and those who did not tolerate 25 mg spironolactone once daily had the dosing frequency reduced to every other day. The primary end-point was all cause mortality. The trial was discontinued early, after a mean follow-up of 24 months as the interim analysis demonstrated the efficacy of spironolactone. There were 386 (46%) deaths in the placebo groups compared with 284 (35%) deaths in the spironolactone group; relative risk of death 0.70 (95% CI 0.60 to 0.82; p<0.001). This 30% reduction in risk was attributed to a lower risk of death from progressive heart failure and sudden death from cardiac causes. Spironolactone also significantly reduced the frequency of hospitalisation from worsening heart failure and significantly improved heart failure symptoms (p<0.001). Gynaecomastia or breast pain was reported in 10% of men in the spironolactone group (61/603) compared with 1% (9/614) in the placebo group (p<0.001). The incidence of serious hyperkalaemia was low in both groups (<2%).

Posology for severe heart failure included on the SmPC is consistent with RALES.

NICE guideline NG106 recommends offering an MRA in addition to an ACE inhibitor (or angiotensin II receptor blocker) and β-blocker to people who have heart failure with reduced ejection fraction if they continue to have heart failure symptoms (NICE, 2018). Before and after starting an MRA and after each dose adjustment serum sodium and potassium should be measured along with an assessment of renal function. Blood pressure should be measured in accordance with NICE guidance. Once target or maximum tolerated dose of the MRA is reached treatment should be monitored monthly for 3 months and then at least every 6 months and at any time the patient becomes acutely unwell. The guidance does not distinguish between MRAs but the literature makes the case for combining an evidence-based approach with personalised medicine in deciding which MRA to use (Iqbal et al., 2014).

There is a lack of clinical trial data in children with heart failure but using a pathophysiological approach spironolactone is advocated at a low, non-diuretic dosage in combination with bisoprolol and lisinopril (Recla et al., 2019).

2.5.4.2 Hepatic Cirrhosis with Ascites and Oedema

Spirolactone has long been the first line therapy of ascites in cirrhosis (Gerbes, 1993) due to the underlying pathophysiology that leads to ascites formation (Wong, 2012). Cirrhosis and portal hypertension stimulate peripheral arterial vasodilation, to compensate; renin, aldosterone, noradrenaline and vasopressin are increased which leads to renal vasoconstriction with a gradual increase in sodium and water retention. The excess fluid is preferentially retained in the peritoneal cavity.

The presence of ascites in patients with cirrhosis is associated with a poor prognosis due to predisposition to other complications. Restriction of dietary sodium and bed rest is effective in

only about 10% patients (Gerbes, 1993) so the majority of patient require diuretic therapy with either spironolactone alone or in combination with a loop diuretic such as furosemide.

Urinary Na⁺/K⁺ ratio is used to determine the starting dose of spironolactone based on the study by Eggert (1970) who demonstrated that patients with a ratio greater than 1 responded well to 100 mg/day of spironolactone whereas those with a ratio less than 1 required larger doses (generally 200 – 300 mg/day). The study demonstrated that individually regulating spironolactone doses in patients with cirrhosis and ascites was effective in all treated patients (n=14; 11 of which received spironolactone alone).

The diuretic effect of spironolactone can be apparent within 48 hours but peak effects are not usually achieved until after 2 weeks treatment due to the impaired metabolism of spironolactone in cirrhotic patients.

Spirolactone monotherapy (starting dose 100 mg, increased to 400 mg) is recommended by The British Society of Gastroenterology in collaboration with the British Association for the Study of the Liver in patients with the first presentation of moderate ascites. In those patients with recurrent severe ascites and if faster diuresis is needed, combination of spironolactone and furosemide is recommended (Aithal et al., 2021).

2.5.4.3 Malignant Ascites

Efficacy of spironolactone in malignant ascites was demonstrated by Greenway et al., (1982).

2.5.4.4 Nephrotic Syndrome

Nephrotic syndrome is defined by the presence of proteinuria, oedema, hyperlipidaemia and hypoalbuminaemia. Spirolactone is used as a diuretic to reduce oedema.

2.5.5.5 Diagnosis and Treatment of Primary Aldosteronism

Primary aldosteronism is characterised by excessive production of aldosterone caused most commonly by benign bilateral adrenal hyperplasia (65-70%) and unilateral adrenal adenoma (30-35%). Other rarer causes include adrenal carcinoma, familial hyperaldosteronism and idiopathic hyperaldosteronism (Funder et al., 2016). Hypertension due to marked hypokalaemia, sodium and water retention develop in the majority of patients and may be the only sign of hyperaldosteronism. Studies have shown that primary aldosteronism is present in 5-13% of patients with hypertension and 14-23% of patients with resistant hypertension (Weiner, 2013). In patients with primary aldosteronism there is a higher risk of cardiovascular and renal damage than matched (age, sex, blood pressure) essential hypertensives (Funder, 2020). If the disease is unilateral, surgery is often most effective with treatment indicated for those not suitable for surgery. Despite new therapeutic approaches spironolactone is considered the cornerstone of treatment for bilateral or idiopathic hyperaldosteronism (Funder, 2020) and is used preoperatively to reduce blood pressure and address electrolyte imbalances.

Spirolactone may be used in the diagnosis of primary aldosteronism (Skluth & Gums, 1990) but other diagnostic tests are now advocated (Funder et al., 2016).

Following confirmatory diagnosis of primary aldosteronism where spironolactone treatment is indicated, treatment is commenced with modest doses at first, which are titrated slowly. Although doses <200 mg/day have been shown to be sufficient for some patients most require 200-400 mg/day (Skluth & Gums, 1990). In patients with primary aldosteronism blood pressure reductions of 0.5 – 0.7 mmHg per mg spironolactone have been reported (Weiner, 2013). Due to the delay in response, dose adjustments are recommended to be done monthly.

Spironolactone has been shown to have a greater antihypertensive effect in hypertension associated with primary aldosteronism than eplerenone, a more selective MRA (Parthasarathy et al., 2011). In this multicentre, randomised, double-blind, active-controlled, parallel group study patients meeting the biochemical criteria for primary aldosteronism were randomised to receive either spironolactone (75-225 mg/day) or eplerenone (100-300 mg/day) for 16 weeks after a single-blind run-in period, using a titration-to-effect design. Changes from baseline in diastolic blood pressure were significantly greater for spironolactone than eplerenone (difference -6.9 mmHg, 95% CI -10.6 to -3.3; $p < 0.001$). Thus, spironolactone is the primary MRA in patients with primary aldosteronism with bilateral adrenal disease with eplerenone an alternative (Funder et al., 2016).

2.5.4.6 Other indications

Hypertension

Spironolactone has been shown to be effective in reducing blood pressure when used as a monotherapy (Batterink et al., 2010) and in combination (Iqbal et al., 2014) in essential hypertension. A Cochrane review in 2010 attempted to determine the effect of spironolactone on mortality and morbidity as well as quantifying the antihypertensive effect when used alone for hypertension (Batterink et al., 2010). The meta-analysis included 5 cross-over studies ($n=137$) conducted between 1966 and 1991 and provided a mean reduction in systolic blood pressure of 20.09 mmHg (95% CI 16.58 to 23.06; $p < 0.00001$) and a 6.75 mmHg (95% CI 4.8 to 8.69; $p < 0.00001$) reduction in diastolic blood pressure. There was a lack of evidence to establish a dose-response relationship and no evidence of effects on clinical outcomes given the small sample size and quality of the evidence. The authors concluded spironolactone doses of 25 to 100 mg/day are reasonable for hypertension. In the UK the current NICE guideline NG136 recommends low-dose spironolactone as a Step 4 treatment for adults with resistant hypertension and a blood potassium level of 4.5 mmol/L or less, although not all spironolactone preparations are licensed for this indication (NICE, 2019).

Spironolactone has also been used in resistant hypertension and the most recent meta-analysis of 12 trials ($n=1655$ patients) demonstrated that spironolactone can result in substantial blood pressure reduction in patients with resistant hypertension at 3 months (Chen et al., 2020).

Heart Failure with Preserved Ejection Fraction

Due to uncertainty surrounding the use of MRAs in heart failure with preserved ejection fraction, Kapelios et al., (2019) assessed the effect of MRAs on cardiac function (echocardiographic, functional and systemic parameters) in this group of patients in a systematic review and meta-analysis. They identified and evaluated 9 trials involving 1164 patients (558 in the MRA group, 576 in the control/placebo group). Spironolactone was the administered MRA in 7 of the 9 trials. MRA treatment was shown to significantly improve indices of cardiac structure and function, increase serum potassium and decrease blood pressure but decrease 6-minute walk distance. Results were promising but the authors concluded larger prospective studies are needed to clarify MRA effects in patients in heart failure with preserved ejection fraction.

Dermatological Indications

Spironolactone is used in a number of off-label dermatological indications (Searle et al., 2020). Treatment aims to reduce androgen-mediated conditions including acne, hidradenitis suppurativa, female pattern hair loss and hirsutism. As with other indications starting dose is low and titrated up dependent upon tolerability and efficacy.

2.5.5 OVERVIEW OF SAFETY

The safety profile of spironolactone is well characterised due to its clinical use over the past 60 years. At low doses (<150 mg/day) adverse events are generally mild and infrequent (Skluth & Gums, 1990). Due to its structural relationship to progesterone spironolactone is associated with a well-established risk of anti-androgenic effects; sexual dysfunction and painful gynaecomastia in men, menstrual irregularities in women. These adverse effects often account for poor compliance with spironolactone, particularly among men which is reported to be around 30% (Funder, 2020). The incidence of gynaecomastia is dose and duration of treatment related (Skluth & Gums, 1990).

Hyperkalaemia is associated with increased all-cause mortality at a level >5.5 mmol/L. The effect of spironolactone is additive to other drugs that inhibit the renin-angiotensin pathway such as ACE inhibitors and angiotensin receptor blockers (ARB). Hyperkalaemia is dose dependent with a 13.5% risk of hyperkalaemia in patients on 25 mg and 41.4% risk in patients on 50 mg (Pitt et al., 1999). In 2016 the MHRA issued a Drug Safety Update concerning the potential risk of fatal hyperkalaemia in patients taking spironolactone and renin-angiotensin system drugs (MHRA, 2021). This stated that concomitant use of spironolactone with ACE inhibitors or ARB increased the risk of severe hyperkalaemia, particularly in patients with marked renal impairment, and should be used with caution. The update was based on the increasing number of spontaneous reports.

The solvent used in the spironolactone non-aqueous solution is MCT, a mixture of fatty acids. Chronic toxicological studies in animals have shown no harmful adverse effects associated with MCT following oral and parenteral administration, inhalation or intraperitoneally (Rowe 2012). In addition, non-clinical studies have indicated that MCT do not have the potential to be mutagenic, carcinogenic or reproductive toxins. Fatty acids are an endogenous part of every living cell and are an essential dietary requirement. In the UK, the Department of Health have set dietary reference values for fatty acids and recommend that total fatty acid intake should average 30% of total dietary energy including alcohol. This equates to about 100 g of fatty acids per day or 1.7 g of fatty acids per kg body weight per day. There is 9.34 g of fatty acids in 10 mL of both strength products, equivalent to approximately 10% of the recommended total fatty acid daily intake. Many of the fatty acids and their salts are listed as generally recognised as safe and the WHO set an unlimited acceptable daily intake (ADI) for the salts of myristic, palmitic and stearic acids. Rosemont currently have a Marketing Authorisation for a clonazepam solution containing MCT (00427/0157-8) which was granted in December 2011 and no safety issues have been raised concerning MCT.

There were no serious adverse events or treatment-emergent adverse events attributed to spironolactone during the bioequivalence study, [REDACTED]

Adverse Events in Heart Failure

The key adverse event data from the RALES study is summarised in Table 25-10. Overall there was no difference in the incidence of adverse events between the patients receiving spironolactone and those receiving placebo but there was a significant difference in the incidence of gynaecomastia or breast pain in men ($p < 0.001$). This contributed to patients discontinuing spironolactone treatment (2% of spironolactone patients discontinued due to gynaecomastia or breast pain compared with 0.2% of placebo patients ($p = 0.006$)). There was no significant difference in the incidence of serious hyperkalaemia between groups ($p = 0.42$) but occurred most frequently with daily doses of 50 mg or more (Pitt et al., 1999).

Table 25-10 Overview of Significant Spirolactone Adverse Events in Heart Failure

Adverse Event	Placebo (n=841)	Spirolactone (n=822) Mean dose 26 mg	P value
One of more event	667 (79)	674 (82)	0.17
Discontinuation due to an AE	40 (5)	62 (8)	-
Endocrine Disorders	26 (3)	84 (10)	
Gynaecomastia on men	8 (1)	55 (9)	<0.001
Breast pain in men	1 (0.1)	10 (2)	0.006
Gynaecomastia or breast pain in men	9 (1)	61 (10)	<0.001
Serious hyperkalaemia (>6 mmol)	10 (1)	14 (2)	NS

There were 614 mean in the placebo group and 603 in the spironolactone group

Abbreviations: AE = adverse event; n = number of subjects; NS = not significant

Source: Table 4 from Pitt et al., 1999

Adverse events in Hypertension

In patients with hypertension and evidence of primary aldosteronism more patients receiving spironolactone developed gynaecomastia (21.2 versus 4.5%; $p=0.033$) and female mastodynia (21.1 versus 0.0%, $p=0.026$) than epleronone (Parthasarathy et al., 2011).

From the most recent meta-analysis of 12 trials (n=1655 patients) in resistant hypertension (Chen et al., 2020) the mean change in serum potassium was defined as the safety outcome. Compared with placebo spironolactone increased serum potassium (weighted mean difference 0.2, 95% CI 0.05 to 0.35; $p<0.01$) but compared with the other control treatment groups (alternative medication, no treatment, or renal denervation).

Studies using spironolactone in arterial hypertension have demonstrated it is generally well tolerated with development of hyperkalaemia uncommon even when used concurrently with an ACE inhibitor (or ARB) and a β -blocker (Lainscak et al., 2015).

Adverse events in Dermatological Conditions

Spirolactone is reported to be well tolerated in dermatological indications. Adverse events include hypotension, diuresis, menstrual irregularities, nausea, diarrhoea, breast tenderness, fatigue and light-headedness. There appears to be no increased risk of hyperkalaemia in healthy young women taking spironolactone for acne. Spirolactone appears safe for long-term use with limited electrolyte monitoring required, particularly in patients aged 45 years or less (Searle et al., 2020).

Despite the hypothesis that spironolactone may increase oestrogen levels and increase the risk of hormone-responsive cancers a recent review concluded there was no consistent evidence of an increased risk of female breast cancer (Rozner et al., 2019). Therefore there is potential for the use of spironolactone for alopecia and hirsutism in breast cancer patients.

2.5.5.1 Safety in Special Populations

Paediatric Population

There is a lack of evidence-based clinical trial paediatric data. Dosage recommendations are based upon clinical experience and case studies. Initial dosing should start low and be titrated in response to tolerability and efficacy. Use of spironolactone in the paediatric population should be under the supervision of a paediatric specialist. Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

Elderly

Severe hepatic and renal impairment may alter spironolactone's metabolism and excretion so care should be taken in elderly patients with hepatic and/or renal impairment. It is recommended that treatment is started with the lowest dose and titrated upwards as required to achieve maximum benefit.

Fertility, Pregnancy and Lactation

Based on non-clinical data, there is potential risk of feminisation of male foetuses therefore spironolactone should only be used in pregnancy where the expected benefits outweigh the potential hazard.

Metabolites of spironolactone cross into breast milk therefore if spironolactone is considered essential for someone who is breastfeeding an alternative method of infant feeding should be instigated.

2.5.5.2 Drug Interactions

The known drug interactions of spironolactone are detailed on the SmPC.

Spironolactone cannot be co-administered with other potassium conserving diuretics and potassium supplements should not be given routinely with spironolactone due to the risk of hyperkalaemia.

Concomitant use with trimethoprim/sulfamethoxazole (co-trimoxazole) may also results in hyperkalaemia.

As previously stated the concomitant use of spironolactone with ACE inhibitors or ARBs increased the risk of severe hyperkalaemia, particularly in patients with marked renal impairment, and should be used with caution

Potential of hypertensive effects need to be considered when spironolactone is added to the antihypertensive regime and the dosage of other antihypertensive medications may need to be adjusted.

Spironolactone can alter the pharmacokinetics of digoxin (Marcus, 1985). Plasma concentrations of digoxin are increased through inhibition of the tubular secretion of digoxin. This results in a decrease in renal and extra-renal clearance of digoxin. Spironolactone also interferes with immunoassays for serum digoxin levels (Dollery, 1991).

As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone they should not be used concurrently

Through the inhibition of intrarenal synthesis of prostaglandins non-steroidal anti-inflammatory drugs (NSAIDs) may attenuate the natriuretic effects of diuretics. The diuretic effect of spironolactone has been shown to be affected by co-administration with an NSAID.

Spiroinolactone reduces vascular responsiveness to noradrenaline so caution is required in patients subjected to regional or general anaesthesia while being treated with spiroinolactone.

Spiroinolactone enhances the metabolism of antipyrine.

2.5.5.3 Overdosage

Overdosage with spiroinolactone may cause drowsiness, mental confusion, nausea, vomiting, dizziness and diarrhoea. Hyperkalaemia and hyponatraemia are unlikely to occur acutely. Symptoms usually respond to withdrawal of the drug, fluid and electrolyte replacement and treatment of hyperkalaemia if appropriate (Dollery, 1991). Further details are included on the SmPC.

2.5.5.4 Risk Management Plan

The Risk Management Plan (RMP) identifies the following adverse events previously reported with spiroinolactone use as important risks:

- Hyperkalaemia
- Renal insufficiency
- Hormonal disturbances (gynaecomastia, voice alteration and impotence)
- Serious skin reaction
- Agranulocytosis

The current product information as detailed on the proposed SmPC and PIL is considered sufficient to minimise these important risks with no additional pharmacovigilance activities beyond adverse event reporting and signal detection deemed necessary. No new safety concerns have been identified.

2.5.6 BENEFITS AND RISK CONCLUSIONS

Spiroinolactone has long been used in clinical practice for cardiovascular and renal disorders. Over the years of its use advances in the understanding of the pathophysiology of these conditions have led to further evidence on the benefits of spiroinolactone treatment. Spiroinolactone continues to be widely used and is included in a number of guidance documents as the first line or adjunctive treatment.

The spiroinolactone non-aqueous solution will provide, for the first time in the UK, a licensed liquid product to those patients who would prefer a liquid formulation or who have swallowing difficulties. The provided dosing pipette will allow for accurate measurement and titration dosing.

Results from the included bioequivalence study demonstrate equivalent systemic exposure between the higher dose strength (50mg/5mL) spiroinolactone solution and the 100 mg Aldactone film-coated reference tablet product but with a slower rate of absorption. The slower rate of absorption is attributed to the liquid fat formulation which takes longer to pass through the stomach to the sites of absorption. However, once absorbed the spiroinolactone from the solution will be distributed, metabolised and eliminated in the same manner as that from the tablet formulation. As there is no correlation with plasma levels of spiroinolactone and clinical effectiveness, this difference in the rate of absorption is not considered clinically relevant, but overall exposure is. The onset of spiroinolactone's action takes several days and is in part due to the time taken for the longer acting active metabolite(s) to reach steady state. In all indications the dose of spiroinolactone is titrated in response to tolerability and effectiveness

allowing a tailored approach for each patient. Thus the observed difference in the rate of absorption will not impact the clinical care of patients in whom spironolactone is indicated.

The safety profile of spironolactone and precautions for use are well known. The MCT vehicle base for the spironolactone solution is a mixture of fatty acids, an essential dietary requirement and therefore unlikely to pose any additional risk. The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The Applicant therefore considers the benefits of being able to offer a licensed oral solution of spironolactone as an alternative to a tablet formulation to outweigh any perceived risk. The products do not present any greater risk to patients than Aldactone tablets.

2.5.7 LITERATURE REFERENCES

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