CLINICAL SUMMARY

Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Spironolactone 25 mg/5ml Oral Solution
Spironolactone 50 mg/5 ml Oral Solution

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Abbreviations

CTD	Common Technical Document
MAA	Marketing authorization application
GCP	Good clinical practice
ICH	International Conference on Harmonization
EC	European Commission
w/v	Weight/volume
CPMP	Committee for Proprietary Medicinal Products.
RPM	Revolutions per minute
QC	Quality Control

2.7.1 Summary of Biopharmaceutic Studies

2.7.1.1 Background and Overview

The objective of CTD Module 2.7.1 is to summarize all relevant information in the MAA dossier with regard to biopharmaceutical studies and associated analytical methods. This section contains a set of tables to assist applicants in review of the data generated in the Bioavailability/Bioequivalence studies, which conducted based on the GCP and ICH-E3 standard guidelines. And these tables are intended to submit in support for a hybrid application according to , Regulation 52 hybrid applications (previously Article 10(3) of Directive 2001/83/EC) and filled in accordance with the section 4.1 of Bioequivalence Guideline (CPMP/EWP/QWP/1401/98 Rev. 1).

Spironolactone is a potassium sparing diuretic used in the treatment of congestive cardiac failure, hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome and in the diagnosis and treatment of primary aldosterism. It can also be used as a supplementary therapy for the treatment of hypertension to lower blood pressure. Spironolactone products have been available on the UK market and widely used in clinical practice for many years since 1957 (Kagawa 1957). The therapeutic use and safety profile of spironolactone is, therefore, well established within the European Union and the UK. A detailed summary of studies from literature is not presented. Applicant conducted a clinical biopharmaceutical study [redacted] n support of this application as additional information.

This document summarizes the pertinent biopharmaceutical characteristics of Spironolactone oral solution (10 mg/mL (At a dose of 5 mL = 50 mg) of Rosemont Pharmaceuticals Limited, United Kingdom to support its application for the marketing approval. The entire data given in these tables should provide the reviewer with an overall view of the formulation development process, the general approach and rationale used in developing the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of comparator product after single oral dose administration in normal, healthy, adult, human subjects under fed condition.

2.7.1.2 Biowaiver Request for Different Strengths

Comparative Pharmacokinetic study is done on strength Spironolactone oral solution 5 mg/ml (at a dose of 5 ml = 25 mg). Due to the well-known risk of adverse events associated with dosing Spironolactone to normal healthy volunteers the company designed the study in line with most other applicants (data as available through the UKPAR system to dose at the 100 mg level).

To justify the applicability of this dose to the other strength in the application the applicant followed the guidance laid down in CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Section 4.1.6 Strength to be investigated.

General biowaiver criteria

The following general requirements must be met where a waiver for additional strength(s) is claimed:

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) *or* i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

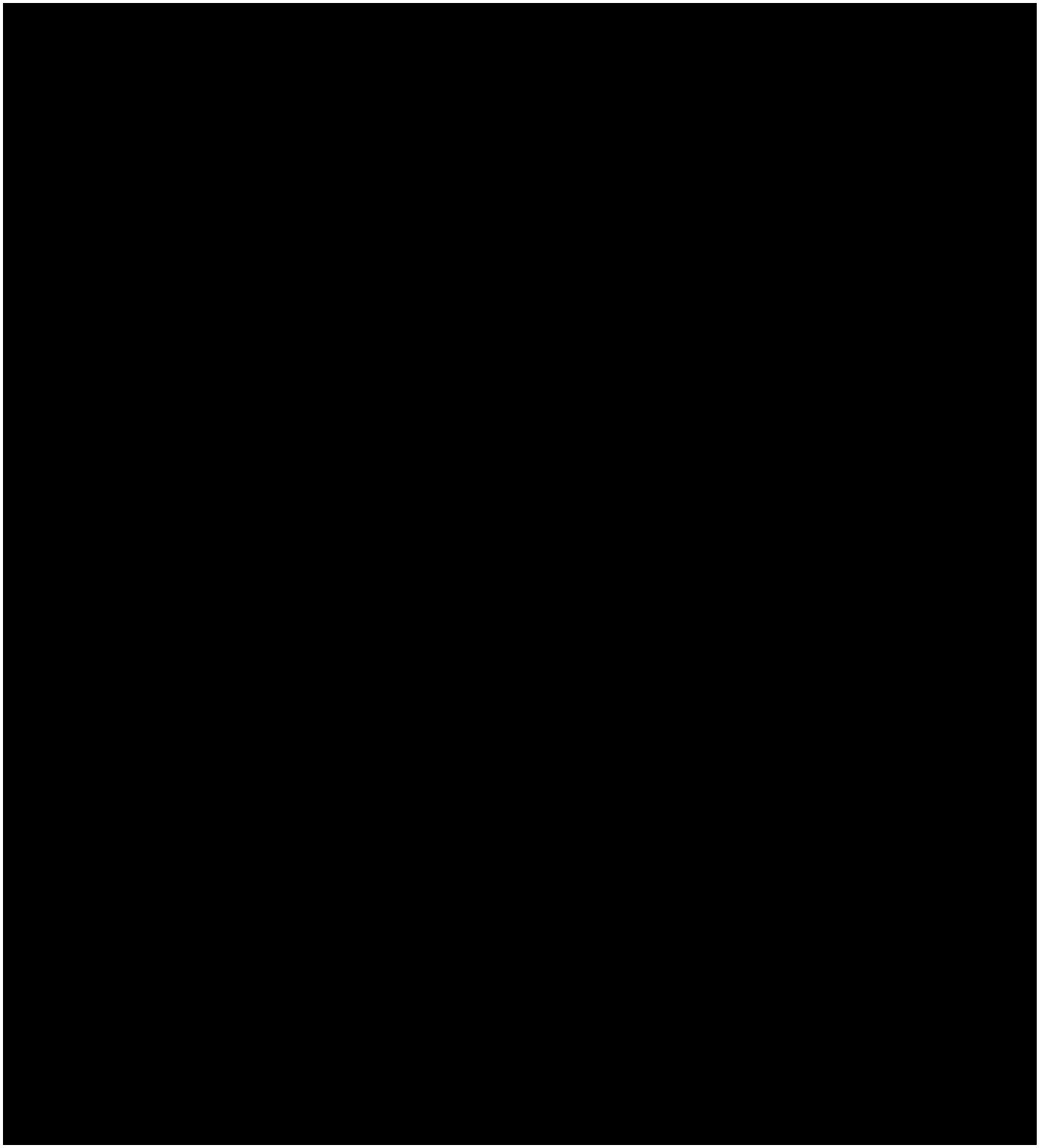
i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content

ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed

iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

[redacted]



2.7.1.3 Summary of Results of Individual Studies

2.7.1.3.1 Bio-Equivalence Trial Information

Test and Reference product information

Table 3: Test and Reference product information

Product Characteristics	Test Product-T	Reference Product-R
Name	Spironolactone Solution 10 mg/mL (50 mg/5 ml)	Aldactone 100 mg Film-Coated Tablets
Strength	10 mg/mL	100 mg
Dosage form	Solution	Tablet
Manufacturer	Rosemont Pharmaceuticals Limited, United Kingdom.	[redacted]
Marketing Authorization Holder	-	Pfizer Limited, Ramsgate Road, Sandwich Kent, CT13 9NJ, United Kingdom.
Batch number	[redacted]	
Batch size (Biobatch)		
Measured content(s) (% of label claim)		
Commercial Batch Size		
Expiry date (Retest date)	29 February 2020	31 May 2023
Location of Certificate of Analysis	5.3.1.2	5.3.1.2
Member State where the reference product is purchased from:		UK
This Product was used in the following trials:	[redacted]	[redacted]

Study Site Description

Table 4: Study Site(s) of [redacted]

	Name	Address	EU Authority Inspection*	
			Year	**Authority**
Clinical Study Site	[redacted]	[redacted]	03 December 2018 - 07 December 2018	MHRA, UK
			02 December 2014 - 06 December 2014	EMA & BfArM, Germany
			16 May 2011-20 May 2011	MHRA, UK
			12 November 2009 -14 November 2009	OGYI, Hungary
Bio-analytical Study Site*	[redacted]	[redacted]	16 December 2019 - 20 December 2019	AEMPS, Spain
			03 December 2018 - 07 December 2018	MHRA, UK
			21 June 2018- 23 June 2018	Infarmed, Portugal
			02 December 2014 - 06 December 2014	EMA & BfArM, Germany
			16 May 2011 - 20 May 2011	MHRA, UK
			12 November 2009 - 14 November 2009	OGYI, Hungary
PK and Statistical Analysis	[redacted]	[redacted]	16 December 2019 - 20 December 2019	AEMPS, Spain
			03 December 2018 - 07 December 2018	MHRA, UK
			02 December 2014 - 06 December 2014	EMA & BfArM, Germany
			16 May 2011 - 20 May 2011	MHRA, UK
			12 November 2009 - 14 November 2009	OGYI, Hungary
Sponsor of the study	Rosemont Pharmaceuticals Ltd.	[redacted]		

*All the inspections were successfully closed.

Table 5: Study description of [redacted]

Study Title	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Spironolactone Solution 10 mg/mL (at a dose of 10 mL = 100 mg) and Aldactone 100 mg Film-Coated Tablets in normal, healthy, adult, human subjects under fed condition
Report Location	5.3.1.2
Study Periods	
Clinical	13 December 2019 - 24 December 2019
Bioanalytical	29 January 2020 to 05 February 2020
Design	
Dose	100 mg
Single/Multiple dose	Single
Number of periods	Two
Two-stage Design	No
Fasting / Fed	Fed
Number of subjects	
- dosed	43
- completed the study	37
- Included in the final statistical analysis of AUC	37
- Included in the final statistical analysis of C_{max}	37

2.7.1.3.2 Study Results

Pharmacokinetic Data for Spironolactone

Table 6: Pharmacokinetic Data for Spironolactone in Project [redacted] (Sponsor Study code: [redacted]

Pharmacokinetic Parameter	Arithmetic Means (± SD)	
	Test Product-T	Reference Product-R
$AUC_{(0-t)}$	387.977 ± 142.3438	356.322 ± 125.1973
$AUC_{0-\infty}$	395.847 ± 143.6077	363.712 ± 126.3634
C_{max}	118.112 ± 49.2420	145.747 ± 64.4736
t_{max}[1]	4.667 (1.333 - 5.517)	1.667 (1.333 - 4.000)

[1]Median (Min - Max).

Additional Pharmacokinetic Data in Project [redacted] (Sponsor Study code: [redacted])

Table 7: Additional Pharmacokinetic Data for Spironolactone

Plasma concentration curves where	Related Information
$AUC_{(0-t)}/AUC_{(0-\infty)} < 0.8$	None
C_{max} is the first point	None
Pre-dose sample > 5% C_{max}	None

Bioequivalence Evaluation of Spironolactone

Table 8: Bioequivalence Evaluation of Spironolactone in Project [redacted] (Sponsor Study code: [redacted])

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	106.7	100.27 - 113.53	15.9
C_{max}	80.5	71.53 - 90.64	30.7

[1]Estimated from the Residual Mean Squares.

2.7.1.3.3 Bioanalytics

Table 9: Bioanalytical method validation

Analytical Validation Report Location	[redacted] Addendum-II, III & V) Appendix No. 16.5.3
This analytical method was used in the following study	[redacted]
Short Description of the Method	Liquid-liquid extraction method, LC-MS/MS
Biological Matrix	Human Plasma
Analyte Location of product certificate	Spironolactone Product certificate of analyte is attached along with method validation report. Appendix No. 16.5.3
Internal Standard (IS)1 Location of product certificate	Spironolactone-d7 Product certificate of Internal standard is attached along with method validation report. Appendix No. 16.5.3
Calibration Range (ng/mL)	0.752 ng /mL to 303.220 ng/ mL (Addendum-II)
Lower Limit of Quantification (ng/mL)	Nominal value : 0.752 ng / mL Accuracy : 100.5 % Precision : 0.8 % (Addendum-II)
QC Concentrations (ng/mL) (LOQ QC, LQC, LMQC, MQC, HQC & DQC)	DQC : 901.839 ng / mL HQC : 239.173 ng / mL MQC : 91.045 ng / mL LMQC : 15.933 ng / mL LQC : 2.231 ng / mL LOQ QC : 0.781 ng / mL (Addendum-II)
Between-run Accuracy	95.2% to 107.4% (Addendum-II)
Between-run Precision	0.9% to 4.8% (Addendum-II)
Within-run Accuracy	95.0% to 110.2% (Addendum-II)
Within-run Precision	0.7% to 2.5% (Addendum-II)

Matrix Factor (MF) (all QC)1 IS normalised MF (all QC)1 C.V. % of IS normalised MF (all QC)1 % of QCs with >85 % and <115 % n.v.1,4 % matrix lots with mean <80 % or >120 % n.v.1,4	HQC 0.8233 (Addendum-II) 1.0024 (Addendum-II) 1.7 % (Addendum-II) 100.0 % 0.0%	LQC 0.8151 (Addendum-II) 0.9833 (Addendum-II) 1.3 % (Addendum-II) 95.0 % 0.0%
Long-term Stability of the Stock Solutions and Working Solutions2 (Observed Change %)	Confirmed up to 08 days within 2 to 8 °C % Mean Ratio: 99.7 % (for stock solution stability of ISTD) (Addendum-II) Confirmed up to 13 days within 2 to 8 °C % Mean Ratio: 101.1 % (for stock solution stability of drug) % Mean Ratio: 101.6 % (for spiking solution stability of drug at lower level)	
Short-term Stability in Biological Matrix at Room Temperature or at Sample Processing Temperature (Observed Change %)	Confirmed up to 17.0 hours (at room temperature) % Change LQC: 5.3 %, HQC: 4.8 % and DQC: -6.5 %	
Long-term Stability in Biological Matrix (Observed Change %) Location	Confirmed up to 433 days at -65 ± 10°C (Addendum-III) % Change DQC: -3.5 %, HQC: 0.3 % and LQC: 10.5 % Confirmed up to 433 days at -22 ± 5°C (Addendum-III) % Change DQC: -4.4 %, HQC: 0.9 % and LQC: 3.7 % Appendix 16.5.3	
Autosampler Storage Stability (Observed Change %)	123.0 hours (within 2 to 8°C) % Change: LQC: 1.5 % and HQC: -1.0 % (Addendum-II)	
Post-preparative Stability (Observed Change %)	2.0 hours (at room temperature) % Change LQC: -0.8 % and HQC: 0.2 %	
Freeze and Thaw Stability (Observed Change %)	5 cycles (at -65 ± 10°C) % Change LQC: 3.4 %, HQC: 5.4 % and DQC: -6.3 %	
Dilution Integrity	901.839 ng / mL diluted up to 5-fold Precision for 1/5 was 0.9 % Accuracy for 1/5 was 95.2 % (Addendum-II)	
Partial Validation3 Location	Addendum-II – The method was partially validated to perform requisite experiments as per global SOP [redacted] and method validation plan No. [redacted] (Version 01) for Change in instrument [i.e. from API 3200 to WATERS XEVO TQS], Change in internal standard [i.e. from Spironolactone-d6 to Spironolactone-d7] & Change in injection volume [i.e. from 20µL to 10 µL] Addendum-III – The method was partially validated to generate long-term stability of analyte in human plasma. Addendum-V – The method was partially validated to update	

	the method and to perform requisite experiments as per SOP [redacted] Appendix No. 16.5.3
Cross Validation(s)3 Location	Not Applicable

[1] Might not be applicable for the given analytical method
[2] Report short term stability results if no long term stability on stock and working solutions are available
[3] These rows are optional. Report any validation study which was completed after the initial validation study
[4] n.v. = nominal value

Table 10: Storage period of Study samples

Study ID[1] and analyte	**Longest Storage Period**
[redacted] and Spironolactone	54 days ([redacted] at -65 ± 10°C

[1] Only pivotal trials

Table 11: Sample Analysis of 0980-18

Analyte	Spironolactone
Total Number of Collected Samples	1762
Total Number of Samples with Valid Results	1760
Total Number of Reassayed Samples[1,2]	03
Total Number of Analytical Runs[1]	22
Total Number of Valid Analytical Runs[1]	21
Incurred Sample Reanalysis	
Number of Samples	147
Percentage of Samples where the Difference between the Two Values was Less than 20% of the Mean for Chromatographic Assays or less than 30% for Ligand Binding Assays	99.3 %

[1] Without incurred samples
[2] Due to other reasons than not valid run

2.7.1.4 Comparison and Analysis of Results across Studies

Comparison of Bioavailability and Pharmacokinetic Profile of Spironolactone

Pharmacokinetic and Bioavailability

Based on the data analyzed from 37 subjects for Spironolactone the pharmacokinetics were assessed for the comparison of Test Product-T versus Reference Product-R.

The pharmacokinetic data were analyzed as per the statistical method defined in the protocol. As per approach specified in the protocol, the data of 37 subjects were analyzed using ANOVA model with the terms Sequence, Subject (Sequence), Formulation and Period as fixed effects.

The test to reference C_{max} ratio (T/R) of geometric least squares mean was 80.5% (90% CI: 71.53 to 90.64%). The test to reference AUC_{0-t} ratio (T/R) of geometric least squares mean was 106.7% (90% CI: 100.27 to 113.53%). The test to reference $AUC_{0-\infty}$ ratio (T/R) of geometric least squares mean was 106.7% (90% CI: 100.36 to 113.45%).

Period effect was found to be statistically significant (i.e. p-value < 0.05) for lntransformed pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Subject (Sequence) effect was found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Overall conclusions:

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.

[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 Cmax and longer Tmax (median Tmax 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 t1/2 3.51 hours and 3.43 hours for the test and reference, respectively).

The lack of equivalence or a lower Cmax 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 and this is discussed in Module 2.5.