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2.7.1 Clinical Summary - Biopharmaceutical and Bioanalytical Data

1 BIOWAIVER REQUEST for DIFFERENT STRENGTHS

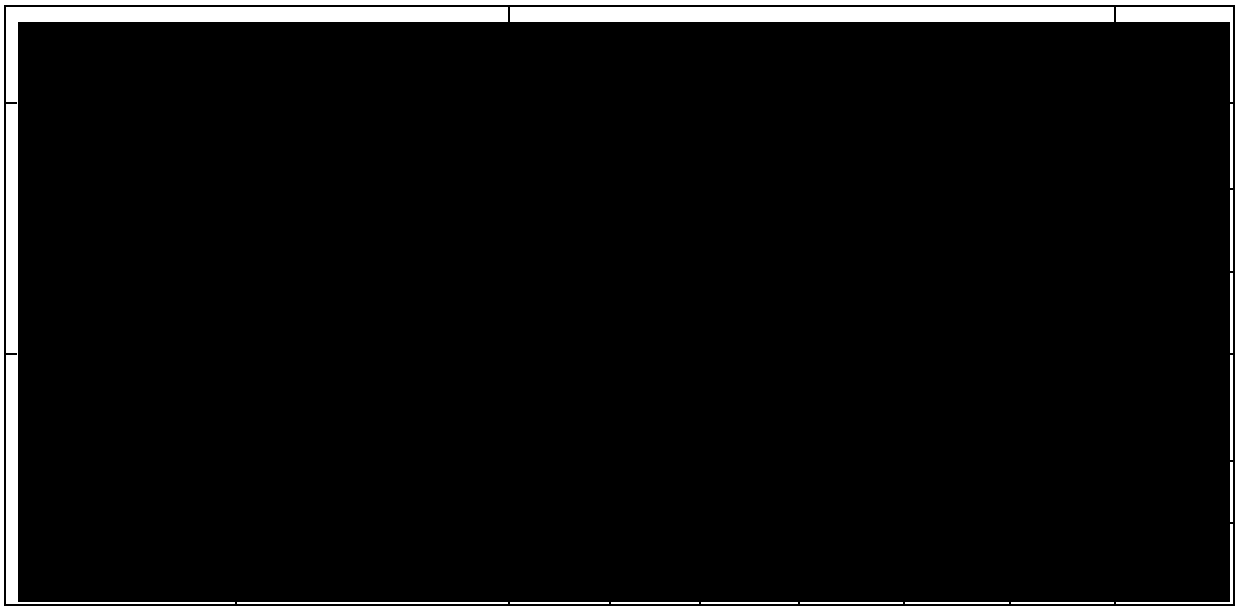
Table 1.1 Qualitative and quantitative composition of the Test product.

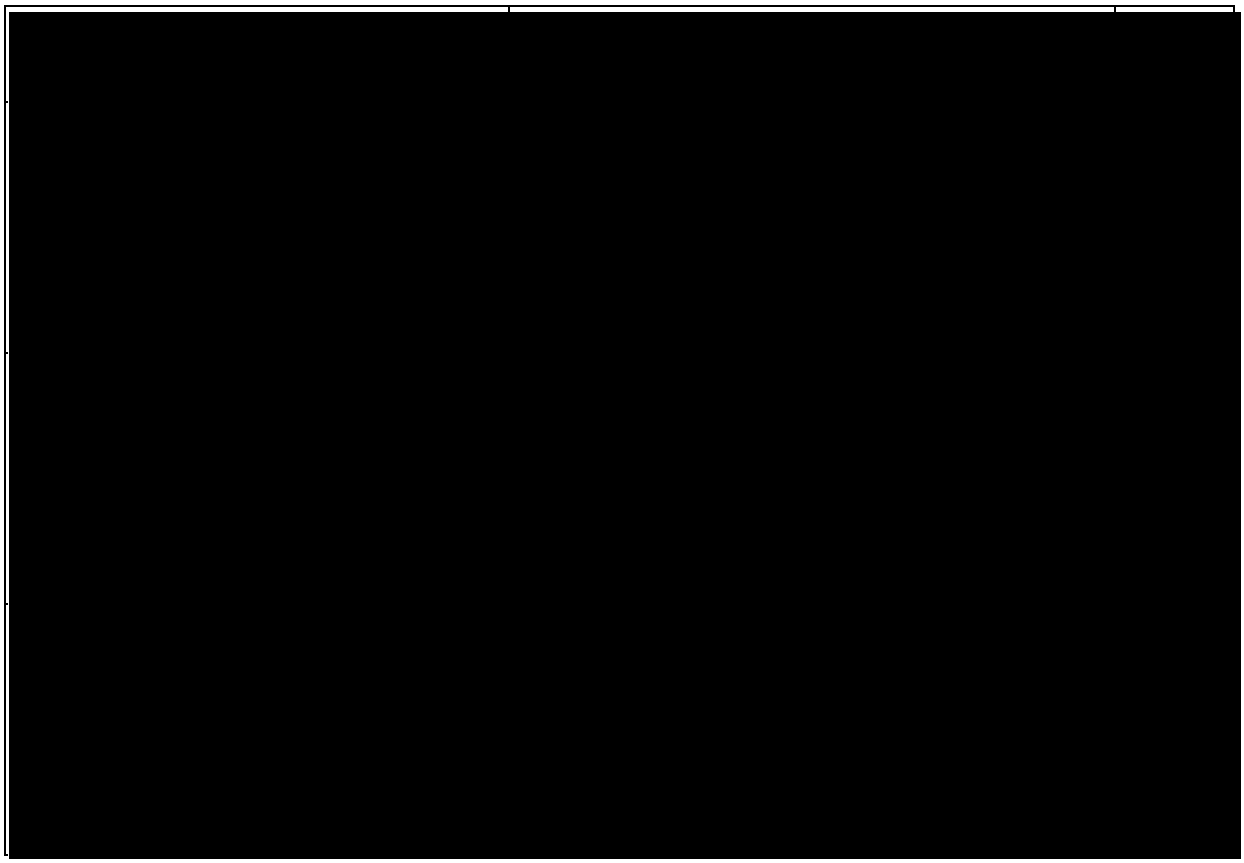
Ingredients/Grade	Function	Specification	Quantity/Tablet (mg)			% w/w
			10 mg Tablets	15 mg Tablets	20 mg Tablets	
Carbimazole	[redacted]	Ph. Eur.	[redacted]	[redacted]	[redacted]	[redacted]
Lactose Monohydrate		Ph. Eur.				
Microcrystalline Cellulose (PH – 102)		Ph. Eur.				
Citric Acid Monohydrate		Ph. Eur.				
Sucrose		Ph. Eur.				
Ferric oxide (Red)		USP/NF				
Magnesium Stearate		Ph. Eur.				
Average weight of Tablet						

Table 1.2 In vitro dissolution data for biowaiver request.

Dissolution testing Site		[redacted]
Location		[redacted]
Dissolution Conditions	Apparatus	[redacted]
	RPM	[redacted]
	Medium	[redacted]
	Volume	[redacted]
	Temperature	[redacted]
	Surfactant	[redacted]

[redacted]





2 BIOEQUIVALENCE TRIAL INFORMATION

Table 2.1 Test and Reference product information

Product Characteristics	**Test product**	**Reference Product**
Name	Carbimazole 20 mg Tablets	NeoMercazole 20 mg Tablets
Strength	20 mg	20 mg
Dosage form	Tablet	Tablet
Manufacturer	[redacted]	
Batch number		
Batch size (Biobatch)		
Measured content(s)[1] (% of label claim)		
Commercial Batch Size		
Expiry date (Retest date)		
Location of Certificate of Analysis		
Member State where the reference product is purchased from:		
This product was used in the following trials:		

Table 2.2 Study Site(s) of Carbimazole Study# [redacted]

	Name	Address	EU Authority Inspection	
			Year	Authority
Clinical Study Site	[redacted]	[redacted]	2007	MPA-Sweden
			2008	AFSSAPS- France and BASG-Austria
			2012	MHRA-UK and NOMA-Norway
			2015	MHRA-UK
Bioanalytical Study Site and statistical Facility	[redacted]	[redacted]	2015	MHRA-UK
Sponsor of the study	[redacted]	[redacted]		

Table 2.3 Study description of Carbimazole Study# [redacted]

Study Title: A Randomized, Open Label, Balanced, Two Treatment, Two period, Two Sequence, Single Dose, Crossover Bioequivalence Study of Carbimazole 20 mg Tablets of [redacted] with NeoMercazole 20 mg Tablets of [redacted] in Normal, Healthy, Adult, Human Subjects under Fasting Conditions.

Report Location:

m5\5.3.1.2, Clinical study report (Page no. 01 to 56)

Study Periods

Clinical:

Period-I: 15 March 2017 - 17 March 2017

Period-II: 29 March 2017 - 31 March 2017

Clinical Completion Date: 31 March 2017

Bioanalytical:

Date of initiation of subject sample analysis: 18 April 2017

Date of completion of subject sample analysis: 28 April 2017

Design:

Dose: Single oral dose (1 x 20 mg Tablet) of test product or reference product in each study period.

Single/Multiple dose: Single dose

Number of periods: Two

Two-stage design: No

Fasting/ Fed: Fasting

Number of subjects

- dosed: Period I- 24
  Period II- 22
- completed the study: 22
- included in the final statistical analysis of AUC: 22
- included in the final statistical analysis of C_{max}: 22

3 RESULTS

Table 3.1A Pharmacokinetic data for Carbimazole in Study# [redacted]

Pharmacokinetic parameter	Arithmetic Mean (±SD)	
	Test Product	Reference Product
$AUC_{(0-t)}$ (ng*hr/mL)	2461.000 ± 529.186	2342.362 ± 647.507
C_{max} (ng /mL)	327.002 ± 79.329	288.379 ± 76.895
t_{max}[1] (hrs)	0.660 (0.330 - 1.250)	0.830 (0.330 – 2.000)
$AUC_{(0-inf)}$	2764.413 ± 637.005	2625.707 ± 744.682

[1]Median (Min, Max)

Table 3.2 Additional pharmacokinetic data for Carbimazole in Study# [redacted]

Plasma concentration curves where	**Related information**
- $AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$[1]	Subject no. [redacted] Period I, Reference product Subject no. [redacted] Period I, Reference product
- C_{max} is the first point	None
- Pre-dose sample > 5% C_{max}	None

[1] Only if the last sampling point of $AUC_{(0-t)}$ is less than 72h

Table 3.3 Bioequivalence evaluation of Methimazole in Study# [redacted]

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Ref**	**Confidence Intervals**	**CV%**[1]
$AUC_{(0-t)}$	107.9244	99.2993 - 117.2987	16.1204
C_{max}	114.5726	105.0454 - 124.9639	16.8117

[1] Estimated from the Residual Mean Squares

4 BIOANALYTICS

Table 4.1A Bioanalytical method validation for Carbimazole

Analytical Validation Report Location (s)	[redacted] Module 5314, analytical-validation-report
This analytical method was used in the following studies:	[redacted]
Short description of the method	[redacted]
Biological matrix	Human plasma
Analyte Location of product certificate	Methimazole Module 5314, certificate-of-analysis
Internal standard (IS) Location of product certificate	[redacted] Module 5314, certificate-of-analysis
Calibration Concentrations (Units)	[redacted]
Lower Limit of Quantification (Units)	[redacted]
QC concentrations (Units)	[redacted]
Between - run accuracy	[redacted]
Between - run precision	[redacted]
Within- run accuracy	[redacted]

Within- run precision	[redacted]
Matrix factor (MF) IS normalized (%CV)	LQC: [redacted] HQC: [redacted]
Long term stability of the stock solution and working solution (observed change %) Location	[redacted] "Method validation report" (Page No. 66 of 86) of Appendix 16.2.5.1 Bio-analytical Study Report [redacted] "Method validation report" (Page No. 72 of 86) of Appendix 16.2.5.1 Bio-analytical Study Report
Short Term stability in biological matrix at room temperature or at sample processing temperature (observed change %)	Short Term stability in biological matrix at room temperature (Bench top stability) [redacted]
Long Term stability in biological matrix (observed change %) Location	[redacted] "Addendum to Method validation report, Addendum 01" (Page Nos. 33 and 34 of 38) of Appendix 16.2.5.1 Bio-analytical Study Report [redacted]

	"Addendum to Method validation report, Addendum 01" (Page Nos. 35 and 36 of 38) of Appendix 16.2.5.1 Bio-analytical Study Report
Autosampler storage stability (Observed change %)	[redacted]
Post - preparative stability (or Processed Sample Stability) (Observed change %)	Post - preparative stability (Processed sample stability) [redacted]
Freeze and thaw stability (Observed change %)	[redacted]

Partial validation Location	[redacted] Module 5314, analytical-validation-report "Addendum to Method validation report, Addendum 01" (Page No. 01 to 38) of Appendix 16.2.5.1 Bio-analytical Study Report [redacted]
Cross Validation Location	[redacted]

Table 4.2 Storage period of study samples

Study ID[1] and analyte	Longest storage period
[redacted] and Methimazole	[redacted]

[1]Only pivotal trials

Table 4.3 Sample analysis of Carbimazole in Study# ARL/17/037

Analyte	Methimazole
Total numbers of collected samples	[redacted]
Total numbers of samples with valid results	[redacted]
Total numbers of reassayed samples[1,2]	[redacted]
Total numbers of analytical runs[1]	[redacted]
Total numbers of valid analytical runs[1]	[redacted]
Incurred sample reanalysis	
Number of samples	[redacted]
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	[redacted]

[1] Without incurred samples