Australian Government
Department of Health
Therapeutic Goods Administration

TGA use only

This form, when completed, will be classified as '**For official use only**'.
For guidance on how your information will be treated by the TGA see: Treatment of information provided to the TGA at <https://www.tga.gov.au/treatment-information-provided-tga>.

Bioequivalence Study Information Form (BSIF)

- Refer to guidance document 'Completing the Bioequivalence Study Information Form' when completing the template
- **Do not** include any text in fields or text boxes indicated for "**TGA use only"**.

For more information, refer to TGA website regarding bioequivalence data summary templates

1 Summary

1.1 Pharmacokinetic Properties

What is the therapeutic dose range?

Were linear pharmacokinetics observed over the dose range?

Yes ☐ ▶ Provide source of the evidence:

No ☐ ▶ Detail when non-linearity occur at certain concentration(s) and any known explanations:

What were the other relevant pharmacokinetic characteristics of the drug substance(s)?

1.2 Summary of bioequivalence studies performed

Provide a brief description of each comparative bioavailability study included in the submission.

1.3 Biowaivers for strength(s) not tested in bioequivalence studies

Were *in vivo* bioequivalence studies submitted for all product strengths included in the application?

Yes ☐ ▶ Go to section 2 Clinical study report

No ☐ ▶ Provide details below.

Which product strengths were not tested in bioequivalence studies?

Are these product strengths not tested in bioequivalence studies, systemically active immediate release oral dosage forms?

Yes ☐ ▶ Complete the additional strength biowaiver template for all other strengths not covered in the bioequivalence study.

Go to section 2 Clinical study report

No ☐ ▶ Provide details below.

List the name and location of the documents provided for waiving bioequivalence studies for systemically active products, that are **not** immediate release oral dosage forms (e.g. patches or modified release oral dosage forms).

TGA use only – Comments from review of Section 1

2 Clinical study report

Study number	
Study title	
Location of the study protocol	
Start and stop dates for each phase of the clinical study	
Dates of product administration	

2.1 Ethics

Name(s) of the independent ethics committee (IEC) or Institutional review board (IRB)	
Approval date of the final protocol	
Approval date of the final consent form	
Location of the ethics approval letter	
Location of the statement that study was performed in accordance with the Declaration of Helsinki	
Location of a reference (blank) copy of the informed consent form	

2.2 Investigators and study administrative structure

Name of principal investigator(s)

Location of the principal investigator(s) signed c.v.

Site details

	Name of the site	Full address of the sites
Clinical facility		
Clinical laboratories		
Analytical laboratories		
Company performing pharmacokinetic/ statistical analysis		

2.3 Study objectives

Provide details of study objectives

2.4 Investigational plan

2.4.1 Overall study design and plan – Description

Provide brief description of the overall study design and plan

2.4.2 Selection of study population

2.4.2.1 Inclusion criteria

List the inclusion criteria applied to study subjects

2.4.2.2 Exclusion criteria

List the exclusion criteria applied to study subjects

2.4.2.3 Health verification

Location of the information

Individual data	
Normal/reference values for blood clinical chemistry tests	
Normal/reference values for haematology tests	
Normal/reference values for urinalysis clinical screen tests	

Subject results that were outside of study site normal values	

Criteria used and all tests performed to judge study subject health status

Health verification schedule or dates when the tests were performed

2.4.2.4 Subjects enrolled and the removal of subjects

Number of subjects enrolled in the study	

Do any of the following apply? No ☐► Go to section 2.4.3

Alternates	Yes	☐►	Number of alternates: Reason for including alternates:
Withdrawals	Yes	☐►	Number of withdrawals: Reason for withdrawals:
Dropouts	Yes	☐►	Number of dropouts: Reason for dropouts:

2.4.3 Products Administered

2.4.3.1 Test product

Batch number	
Batch size	
Date of manufacture	
Expiry date	
Potency (assay, % label claim)	
Location of the certificate of analysis (CoA)	

2.4.3.2 Reference Product

Name of the product	
Name and address of the manufacturer	
Market where the product was purchased	
Batch number	
Expiry date	
Potency (assay, % label claim)	
Location of the CoA	

2.4.3.3 Justification of the choice of reference product

Justify the choice of reference product

Location of the reference product confirmation evidence

Photographic images of the reference product carton and primary container labels	
Purchase receipt(s), or signed confirmation in writing where the reference product was purchased	

2.4.4 Selection of doses in the study

How many dosage units comprise a single administered dose?	

2.4.5 Selection and timing of the dose for each subject

Volume and type of fluid consumed with dose	
Interval between doses (i.e. length of washout period)	

Protocol for the administration of food and fluid	
Restrictions on posture and physical activity during the study	

2.4.6 Drug concentration measurements

2.4.6.1 Identify the biological fluid(s) sampled

State the biological fluid(s) sampled

2.4.6.2 Sampling protocol

Number of samples collected per subject	
Volume of fluid collected per sample	
Total volume of fluid collected per subject per phase of the study	
Nominal study sampling times	
Deviations from the sampling protocol	
Location of the summary of the sampling protocol deviations	

2.4.6.3 Sample Handling

Method of sample collection	
Sample handling, work up, and, storage and transportation procedures	

TGA use only – Comments from review of Section 2

3 Study subjects

3.1 Demographic and other baseline characteristics

Study population	
Ethnic origin and gender of subjects	
Subjects with special characteristics	

Summary of the demographic data of the study subjects

	Range	Mean ± SD
Age of the subjects (in years)		
Height of the subjects (in centimetres)		
Weight of subjects (in kilograms)		
BMI of the subjects		

Were there any subjects' BMI outside of 18.5-30 kg/m^2?

No ☐ ▶ Go to the section 3.2

Yes ☐ ▶ Identify these subjects below.

3.2 Subjects who smoke

Did any enrolled subjects in the study smoke tobacco?

No ☐ ▶ Go to the section 3.3

Yes ☐ ▶ Provide details below

Number of smokers included in the study	

Number of cigarettes smoked per day per subject	
Impact to study	

3.3 Concomitant medications

Did any subjects use concomitant medications during the study?

No ☐ ► Go to section 4

Yes ☐ ► Provide details below.

- List the administered concomitant medications by subject number and;
- Discuss the potential consequences for pharmacokinetic and bioanalytical interactions / interferences below

TGA use only – Comments from review of Section 3

4 Protocol deviations

Were there any protocol deviations during the clinical study (excluding sample protocol deviations)?

No ☐ ► Go to the section 5

Yes ☐ ► Provide details below.

Describe any deviations and discuss their implications with respect to bioequivalence below

TGA use only – Comments from review of Section 4

5 Safety evaluation

Were there any adverse events following administration of the test or reference product?

No ☐ ► Go to the section 6

Yes ☐ ► Provide the details below.

Observed adverse events	
Location of adverse event summary	

TGA use only – Comments from review of Section 5

6 Efficacy evaluation – Efficacy results and tabulations of individual study subject's data

6.1 Presentation of data

Location of the information

Tables of mean and individual subject concentrations	
The individual linear and semi-logarithmic subject drug concentration vs. time plots	

Insert the mean linear and semi-logarithmic subject drug concentration vs. time plots below:

6.2 Pharmacokinetic (PK) parameters

6.2.1 Calculation of pharmacokinetic parameters

How were the pharmacokinetic parameters calculated/ obtained for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, the elimination rate constant, and $t_{½}$?

Location of description in protocol on pharmacokinetic analysis

6.2.2 Pharmacokinetic parameters results

Single Dose

Parameter	Test product				Reference product			
	Arithmetic mean	Standard deviation	Minimum & Maximum	Inter-individual coefficient of variation (%)	Arithmetic mean	Standard deviation	Minimum & Maximum	Inter-individual coefficient of variation (%)
AUC_{0-t} (units)								
AUC_{0-inf} (units)								
C_{max} (units)								
t_{max} (units)*								
t½ (units)								

* Median

Multiple Dose

Parameter	Test product				Reference product			
	Arithmetic mean	Standard deviation	Minimum & Maximum	Inter-individual coefficient of variation (%)	Arithmetic mean	Standard deviation	Minimum & Maximum	Inter-individual coefficient of variation (%)
$AUC_{0-\tau}$ (units)								
$C_{max,ss}$ (units)								
$C_{\tau,ss}$ (units)								
$t_{max,ss}$ (units)*								
t½ (units)								

* Median

6.2.3 Ratio of AUC_{0-t} to AUC_{0-inf}

Test product mean ratio of AUC_{0-t} to AUC_{0-inf}	
Reference product mean ratio of AUC_{0-t} to AUC_{0-inf}	
Location of individual ratios	

6.3 Statistical analysis

6.3.1 Statistical analysis calculation

Was the statistical analysis method different to as described in the TGA adopted EU guideline?

No ☐ ▶ Go to the next question in this section 6.3.1

Yes ☐ ▶ Justify the difference in method below.

What was the software used for computing ANOVA?

6.3.2 Geometric means, results from ANOVA, Degrees of Freedom (DF) and intra-subject derived coefficient of variation (CV)

Ensure the following results provided are from the ANOVA (parametric) on the logarithmically transformed AUC_{0-t} and C_{max} and other relevant parameters.

Single Dose

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	Intra-subject CV (%)
AUC_{0-t} (units)						
AUC_{0-inf} (units)						
C_{max} (units)						

Multiple Dose

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	Intra-subject CV (%)
$AUC_{0-\tau}$ (units)						
$C_{\tau,ss}$ (units)						
$C_{max,ss}$ (units)						

6.3.3 Comparison of the results

How did the study results compare with the publicly available data of the reference product and pharmaceutically equivalent products (if any), including mean values, inter- and intra-individual variability?

6.3.4 Statistical Effects

Discuss the potential impact on the study outcome

TGA use only – Comments from review of Section 6

7 Analytical validation report

7.1 Analytical technique

Location of the validation protocol	
Analyte(s) monitored	
Source of the reference standard	
Location of the reference standard CoA	
Internal standard used	
Source of the internal standard	
Location of the internal standard CoA	
Method of extraction	
Analytical technique or method of separation employed	

Method of detection	
Anticoagulant used, if applicable	
Reference citations of the analytical technique or method, if based on a published procedure	
Protocol deviations	

7.2 Selectivity

Address the methods used to verify selectivity and the results	

7.3 Sensitivity

Address the methods used to verify sensitivity methods and the results	

7.4 Carry-over

Summarise the method used to verify carry-over and the results	

7.5 Standard curves

Location of the tabulated raw data	
Location of the back calculated data with descriptive statistics	
Number of calibration standards	
Concentration of calibration standards	
Regression model used including any weighting	
Back-calculated concentrations of the	

calibration standards of the validation runs	

7.6 Quality control samples

Concentrations of the QC samples	
Storage conditions employed for the QC samples prior analysis	

7.7 Precision and accuracy during validation

What was the inter-run accuracy and precision of the calibration standards?

During assay validation	
During assay re-validation (If applicable)	

What were the inter-run and intra-run accuracy and precision of the QC samples?

During assay validation	
During assay re-validation (If applicable)	

7.8 Dilution integrity

Summarise the method used to verify dilution integrity and the results	

7.9 Matrix effect (in case of MS detection)

Summarise the methods used to verify matrix effect and the results	

7.10 Stability

Stability studies	Location of the raw data	Summary of the data
Long-term storage		
Freeze-thaw		
Bench top		

Stability studies	Location of the raw data	Summary of the data
Auto-sampler storage		
Others:		

7.11 Re-injection reproducibility

Summarise the method used to verify re-injection reproducibility and the results	

TGA use only – Comments from review of Section 7

8 Bioanalytical study report

Location of the bioanalytical report for the analysis of the study subject samples	

8.1 Analytical technique

Location of the analytical protocol	
Protocol deviations	
Dates of subject sample analysis	
Longest period of subject sample storage	

Were there any differences between the validated method (including equipment used) described in Section 7 above and the method employed for subject sample analyses?

No ☐ ► Go to the next question in this section 8.1

Yes ☐ ► Provide the differences between the method below.

Were all samples for a given subject (except repeat analyses) analysed together in a single analysis run?

Yes ☐ ► Go to the section 8.2

No ☐ ► List the subjects and justify why below.

8.2 Standard curves

Location of the tabulated raw data	
Location of the back calculated data with descriptive statistics	
Number of calibration standards	
Concentration of calibration standards	
Number of curves run during the study for subject sample analyses	
Descriptive data of the calibration standards including slope, intercept, correlation coefficients	
Back-calculated concentrations of the calibration standards of the study runs	

8.3 Quality control samples

Concentrations of the QC samples	
Date of preparation of the QC samples	
Storage conditions and duration of storage employed for the QC samples prior analysis	

Number of QC samples in each analytical run per concentration	
Percentage of QC samples per run with respect to the total number samples assayed in each run	
Back-calculated concentrations of the QC samples of the study runs	

Were the concentrations of the QC samples similar to those observed during subject sample analysis?

Yes ☐ ► Go to the section 8.4

No ☐ ► Discuss the differences observed below.

8.4 Precision and accuracy

Inter-day precision of back-calculated standards	
Inter-day and intra-day precision and accuracy of QC samples	
Number of subject samples runs that were rejected and reason for each rejection	

8.5 Repeat analysis (re-analysis, re-injection and re-integration)

Do any of the following repeat analyses apply? No ☐ ► Go to the section 8.6

Re-analysed samples	Yes	☐ ►	Percentage re-analysed samples out of total number samples assayed:
Re-injected samples	Yes	☐ ►	Percentage of re-injected samples out of total number samples assayed:
Re-integrated chromatogram samples	Yes	☐ ►	Percentage of re-integrated chromatogram samples out of total number of samples assayed:

Summary details of repeated samples

Sample number	Reason for repeat analysis	Initial value	Re-analysed value	Accepted value	Reason for acceptance

8.6 Incurred sample reanalysis (ISR)

Location of the ISR information	
Number of subject samples included in ISR	
Total number of samples analysed	

What were the acceptance criteria for percent (%) difference?

☐ ≤ 20% ☐ ≤ 30% for ligand binding assays ☐ other:

What was the percentage of the reanalysed samples that met the % difference acceptance criteria?	%
If less than 67% of the repeats, provide explanation:	

8.7 Chromatograms

Location of sample chromatograms	

TGA use only – Comments from review of Section 8

9 Quality assurance

9.1 Internal quality assurance methods

Name of study site	Location of internal quality assurance methods and results

9.2 Monitoring, auditing, inspections

Name of the clinical or bioanalytical site	Name of the monitoring, auditing or inspection report	Location of the report

TGA use only – Comments from review of Section 9

10 TGA's conclusions and questions

TGA's conclusion on individual study

TGA use only – Conclusion on individual study

TGA's Overall conclusions on bioequivalence

TGA use only – Overall conclusions on bioequivalence

List of questions to the applicant

TGA use only – List of questions

11 Applicant’s response to the list of TGA questions

12 TGA’s assessment and decisions

TGA’s assessment of applicant’s responses

TGA use only – Assessment of applicant’s responses to the list of questions

TGA’s decision on the bioequivalence conclusion

TGA use only – Decision on the bioequivalence conclusion