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| **BIOEQUIVALENCE TRIAL INFORMATION FOR VETERINARY MEDICINES** |

This document should be completed by the applicant to ensure the inclusion of all necessary information (in size 11 Arial font – black).

[For the evaluator:

* Primary reviewer’s comments to be added in red.
* Queries to the applicant to be in red and highlighted in yellow.
* Peer reviewer’s comments to be added in blue.
* Once the report has been sent to the second reviewer for comment, deletion of comments and information is not allowed. ~~Strikethrough~~ should be used to show cancellation of a comment.]

[For the applicant: Please complete the table below.]

| **Product information** |
| --- |
| Applicant name | {Licensed Name} |
| Master product application number/s (if allocated) |  |
| Duplicate product application number/s |  |
| Master product proprietary name/s |  |
| Duplicate product proprietary name/s |  |
| Date of application |  |
| Manufacturer (name and address) |  |
| Manufacturer applied for (name and address) |  |
| API manufacturer (name and address) |  |
| API manufacturer applied for (name and address) |  |
| Dosage form |  |
| Batch number and size (test product) |  |
| Date of manufacture (test product) |  |
| Foreign registration status |  |
| Contract Research Organisation (CRO) name  |  |
| IEC (Independent Ethics Committee) |  |
| Study Protocol Number |  |
| Report number |  |
| Study design |  |
| Reference productBatch Number & expiry date |  |
| South African Innovator ProductBatch Number & expiry date |  |
| Study period |  |
| Principal investigator |  |
| Sponsor |  |
| Number of subjects |  |
| Bioequivalence assessment outcome (**For SAHPRA use only**) |  |

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# SUMMARY

## Summary of bioequivalence studies performed

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

## Tabulation of the composition of the formulation(s) proposed for marketing and those used for bioequivalence studies

[State the location of the master formulae in the quality part of the submission.]

[Tabulate the composition of the bio batch using the table below. For solid oral dosage forms, the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any. **Important**: If the formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used.]

|  |
| --- |
| Composition of the batches used for bioequivalence studies |
| Batch number |  |
| Batch size (number of unit doses)[[1]](#footnote-1) |  |
| {Insert comments, if any} |
| Comparison of unit dose compositions and of clinical FPP batches[Duplicate this table for each strength, if compositions are different] |
| Ingredients (and quality standard) | Function | Unit dose (mg) | Unit dose (%) | Bio batch (kg) | Bio batch (%) |
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|  |  |  |  |  |  |
| **Total** |  |  |  |  |
| Equivalence of the compositions or justified differences |  |
| Maximum intended commercial batch size |  |

# BE STUDY REPORT

|  |  |
| --- | --- |
| Study number | {Insert here} |
| Study title | {Insert here} |
| Location of study protocol | {Insert here} |
| Start and stop dates for each phase of the BE study | {Insert here} |
| Dates of product administration | {Insert here} |

## Ethics

[State the name of review committee, date of approval of protocol and consent form and the location of approval letter in the submission.]

[State location in the dossier of a reference copy of the owner informed consent form.]

[Describe animal management and housing prior and during the study to the study]

## Investigators and study administrative structure

|  |  |
| --- | --- |
| Name of principal investigator(s) | {Insert name and location of CV in the dossier} |
| BE study facility  | {Insert name and full mailing address here} |
| Clinical laboratories | {Insert name and full mailing address here} |
| Analytical laboratories | {Insert name and full mailing address here} |
| Company performing pharmacokinetic / statistical analysis | {Insert name and full mailing address here} |

## Study objectives

[Briefly state the study objectives.]

## Investigational plan

### Overall study design and plan — description

[Describe the type of study design employed in 1-2 sentences]

### Selection of study population

#### Inclusion criteria

[List the inclusion criteria applied to subjects.]

#### Exclusion criteria

[List the exclusion criteria applied to subjects.]

#### Health verification

[State location of the individual data included in the submission.]

1. List criteria used and all tests performed to judge health status:

{List here.}

1. Indicate when tests were performed:

{Indicate here.}

1. Study site normal values:

[State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen.]

1. Report any results that were outside of study site normal values:

[State location in submission of the summary of anomalous values.]

#### Removal of trial subjects from trial or assessment

1. Number of subjects enrolled in the study:

[All subjects including alternates, withdrawals, and dropouts.]

1. Alternates:

[Please note: Generally, all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects, describe the procedure of including / excluding the alternates and whether alternates have been included in the study.]

1. Withdrawals / dropouts:

[Identify each withdrawal / dropout by subject and provide the reason for withdrawal / dropout and at what point in the study the withdrawal / dropout occurred.]

### Products administered

#### Test product

1. Batch number, size, date of manufacture and expiry date for the test product
2. Potency (measured content) of test product as a percentage of label claim as per validated assay method

[This information should be cross-referenced to the location of the certificate of analysis in the submission.]

#### Comparator (reference) product

[Append to this template a copy of product labelling (snapshot of the box, on which the name of the product, name and address of the manufacturer, batch number, and expiry date are clearly visible on the labelling.]

1. Name and withdrawal period of the comparator
2. Manufacturer of the comparator product

{Insert here.}

1. Batch number and expiry date for the comparator product

{Insert here.}

1. Purchase, shipment, storage of the comparator product

[Indicate from which company / pharmaceutical distributor the comparator product has been obtained. Clearly indicate in chronological order the steps and dates of shipment/transport from company of purchase to the study site. In addition, the storage conditions should be given. This information should be cross-referenced to location in submission of documents (e.g., receipts) proving conditions.]

1. Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product

[This information should be cross-referenced to the location of the certificate of analysis in the submission.]

1. Justification of choice of comparator product

[Provide a short summary here and cross-reference to location of comprehensive justification in study protocol.]

### Selection of doses in the study

1. State dose administered

[Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets.]

### Selection and timing of dose for each subject

1. State volume and type of fluid consumed with dose

{Insert here.}

1. Interval between doses (i.e., length of washout)

{Insert here.}

1. Protocol for the administration of food and fluid

{Insert here.}

1. Restrictions and housing

{Insert here.}

### Blinding

#### Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so:

|  |  |  |
| --- | --- | --- |
| Study monitors | Yes [ ]  | No [ ] {Provide justification.} |
| Subjects | Yes [ ]  | No [ ] {Provide justification.} |
| Analysts | Yes [ ]  | No [ ] {Provide justification.} |

#### Identify who held the study code and when the code was broken

{Insert here.}

### Drug Concentration Measurements

#### Biological fluid(s) sampled

{Insert here.}

#### Sampling protocol

1. Number of samples collected per subject

{Insert here.}

1. Volume of fluid collected per sample

{Insert here.}

1. Total volume of fluid collected per subject per phase of the study

{Insert here.}

1. List the study sampling times

{Insert here.}

1. Identify any deviations from the sampling protocol

[State location of summary in the submission. Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis.]

#### Sample Handling

1. Describe the method of sample collection

{Insert here.}

1. Describe sample handling and storage procedures

{Insert here.}

|  |
| --- |
| Comments from review of Section 2 – *For SAHPRA use only* |
|  |

# TRIAL SUBJECTS

## Species population and other baseline characteristics

1. Identify study population (i.e., species, breed, healthy subjects or patients, sex)

{Insert here.}

1. Informed owner consent

{Insert here.}

1. Identify subjects noted to have special/unique characteristics and state the notable characteristics

{Insert here.}

1. Range and mean age ± SD of subjects

{Insert here.}

1. Range and mean weight ± SD of subjects

{Insert here.}

|  |
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| Comments from review of Section 3 – *For SAHPRA use only* |
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# PROTOCOL DEVIATIONS

## Protocol deviations during the clinical study

[Describe any such deviations and discuss their implications with respect to bioequivalence.]

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| Comments from review of Section 4 – *For SAHPRA use only* |
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# SAFETY EVALUATION

## Identify adverse events observed

[List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. Identify any deaths and pathology results. State location of this summary in the submission.]

[Discuss the implications of the observed adverse events with respect to bioequivalence.]

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| Comments from review of Section 5 – *For SAHPRA use only* |
|  |

# EFFICACY EVALUATION

Efficacy results and tabulations of individual trial subjects’ data

## Presentation of data

1. State location in submission of tables of mean and individual subject concentrations

{Insert here.}

1. State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

{Insert here.}

## Pharmacokinetic (PK) parameters

1. State how the pharmacokinetic parameters where calculated/obtained for AUC0-inf, AUC0-t, Cmax, Tmax, the elimination rate constant, and t½ (indicate location of description in protocol)

{Insert here.}

1. State whether actual sampling time points were used for estimation of the pharmacokinetic parameters

{Insert here.}

1. Complete the table below:

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Test** | **Reference** |
| **Arithmetic mean** | **Standard deviation** | **Interindividual coefficient of variation (%)** | **Arithmetic mean** | **Standard deviation** | **Interindividual coefficient of variation (%)** |
| AUC0-t (units) |  |  |  |  |  |  |
| AUC0-inf (units) |  |  |  |  |  |  |
| Cmax (units) |  |  |  |  |  |  |
| Tmax (units) |  |  |  |  |  |  |
| t½ (units) |  |  |  |  |  |  |

1. State whether actual sampling time points were used for estimation of the pharmacokinetic Ratio of AUC0-t to AUC0-inf

[State mean ratio for both test and reference, state location in submission where individual ratios can be found]

## Statistical analysis

[State the method of calculation of the 90% confidence intervals for the ratio of test formulation over the reference formulation and indicate how treatment, period, sequence and subjects within sequence were included as factors in the ANOVA. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC0-t and CMAX and other relevant parameters. State software used for computing ANOVA.]

1. Geometric means, results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-subject):

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | Test | Reference | % Ratio of geometric means | 90 % Confidence interval | DF | CV (%) |
| AUC0-t (units) |  |  |  |  |  |  |
| AUC0-inf (units) |  |  |  |  |  |  |
| Cmax (units) |  |  |  |  |  |  |

1. Comparison of the results

[Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), EPARs), and copies of the references used should be appended to this document].

## Discussion of results

[State location of the discussion of the results in the submission.]

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| --- |
| Comments from review of Section 6 – *For SAHPRA use only* |
|  |

# ANALYTICAL VALIDATION REPORT

## Analytical technique

### Validation protocol

[State the location of the validation protocol.]

### Identify analyte(s) monitored

{Insert here.}

### Comment on source and validity of reference standard

{Insert here.}

### Identify internal standard

{Insert here.}

### Comment on source and validity of internal standard

{Insert here.}

### Identify method of extraction

{Insert here.}

### Identify analytical technique or method of separation employed

{Insert here.}

### Identify method of detection

{Insert here.}

### Identify anticoagulant used (if applicable)

{Insert here.}

### If based on a published procedure, state reference citation

{Insert here.}

### Identify any deviations from protocol

{Insert here.}

## Selectivity

[Address the methods to verify selectivity against endogenous/exogenous compounds & results.]

## Sensitivity

[Address the methods to verify sensitivity & results.]

## Carry-over

[Summarize the method to verify carry-over & results.]

## Standard curves

[State location in submission of tabulated raw data and back calculated data with descriptive statistics.]

1. List number and concentration of calibration standards used
2. Describe the regression model used including any weighting
3. List the back-calculated concentrations of the calibration standards of the validation runs (highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)

## Quality control samples

1. Identify the concentrations of the QC samples and the storage conditions employed prior to their analysis

{Insert here.}

## Precision and accuracy during validation

1. Summarise inter-day/inter-run accuracy and precision of the calibration standards during assay validation

{Insert here.}

1. Summarise inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation (if applicable)

{Insert here.}

1. Summarise inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation

{Insert here.}

1. Summarise inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation (if applicable)

{Insert here.}

## Dilution integrity

[Summarise the method to verify dilution integrity & results.]

## Matrix effect (in case of MS detection)

[Summarise methods to verify the matrix effect & results.]

## Stability

[For each section provide the location of the raw data, a description of the methodology employed and a summary of the data.]

1. Summarise data on long-term storage stability

{Insert here.}

1. Summarise data on freeze-thaw stability

{Insert here.}

1. Summarise data on bench top stability

{Insert here.}

1. Summarise data on auto-sampler storage stability

{Insert here.}

1. Summarise data from any other stability studies conducted

[For example, long-term stock solution and working solution stability, short-term stock solution and working solution stability, dry-extract stability, wet-extract stability, stability in blood before sample processing.]

## Re-injection reproducibility

[Summarise the method to verify re-injection reproducibility & results]

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| Comments from review of Section 7 – *For SAHPRA use only* |
|  |

# BIOANALYTICAL STUDY REPORT

[State the location of the bioanalytical report for the analysis of the study subject samples.]

## Analytical technique

[Confirm whether the method is the same as the validated method and whether the same equipment was employed. Identify any differences between the validated method described above in Section 7 and the method employed for subject sample analyses.]

### Analytical protocol

[State the location of the analytical protocol.]

### Identify any deviations from protocol

{Insert here.}

### Dates of subject sample analysis

{Insert here.}

### Longest period of subject sample storage

[Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis.]

### State whether all samples for a given subject were analysed together in a single analysis run

{Insert here.}

## Standard curves

[State location in submission of tabulated raw data and back calculated data with descriptive statistics.]

1. List number and concentration of calibration standards used

{Insert here.}

1. State number of curves run during the study (valid and failed runs, including reasons of failure).

{Insert here.}

1. Summarize descriptive data including slope, intercept, correlation coefficients

{Insert here.}

1. List the back-calculated concentrations of the calibration standards of the study runs (highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)

{Insert here.}

## Quality control samples

1. Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis

{Insert here.}

1. State the number of QC samples in each analytical run per concentration

{Insert here.}

1. List the back-calculated concentrations of the QC samples of the study runs (highlight the values outside of the acceptance range, e.g., 15%)

{Insert here.}

1. Discuss whether the concentrations of the QC sample concentrations are like the concentrations observed in the study samples

{Insert here.}

1. State the percentage of QC samples per run with respect to the total number samples assayed in each run

{Insert here.}

## Precision and accuracy

[Summarise inter-day precision of back-calculated standards and inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis.]

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

1. List re-analysed samples by sample identification and include the following information for each re-analysis: initial value; reason for re-analysis; re-analysed value(s); accepted value; and reason for acceptance

{Insert here.}

1. Report the number of re-analyses as a percentage of the total number samples assayed

{Insert here.}

1. List re-injected samples by sample identification and include the following information for each re-injection: initial value; reason for re-injection; re-injected value; accepted value; and reason for acceptance

{Insert here.}

1. Report the number of re-injections as a percentage of the total number samples assayed

{Insert here.}

1. List re-integrated chromatograms by sample identification and include the following information for each re-integration: initial value; reason for re-integration; re-integrated value(s); accepted value; and reason for acceptance

{Insert here.}

1. Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

{Insert here.}

## Incurred sample reanalysis

[State location in the submission and summarize the results of incurred sample reanalysis, including the number of subject samples included in ISR and the total number of samples analysed in the study.]

## Chromatograms

[State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose, and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas.]

|  |
| --- |
| Comments from review of Section 9 – *For SAHPRA use only* |
|  |

# QUALITY ASSURANCE

## Internal quality assurance methods

[State locations in the submission where internal quality assurance methods and results are described for each of study sites (see table in section 2.2).]

## Monitoring, auditing, inspections

[Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each study site (see table in section 2.2).]

|  |
| --- |
| Comments from review of Section 10 – *For SAHPRA use only* |
|  |

|  |
| --- |
| Conclusions and recommendations – *For SAHPRA use only* |
|  |

EVALUATORS

|  |  |  |  |
| --- | --- | --- | --- |
| **Evaluator** | **Full name** | **Signature** | **Date** |
| Primary reviewer |  |  |  |
| Peer reviewer |  |  |  |

1. . Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules / tablets whichever is greater). Manufacturing method should be the same as for production scale. [↑](#footnote-ref-1)