This form is not to be used if a biowaiver is requested for additional strength(s) of a submitted product(s), in which case a separate "*Biowaiver Application Form: Additional Strengths, BOMRA-ER-VET-P02-F06*" should be used.

Administrative data

1. INN of active ingredient(s)
<< *Please enter information here* >>

2. Dosage form and strength
<< *Please enter information here* >>

3. Product MRA Reference number *(if product dossier has been accepted for PQTm assessment)*
<< *Please enter information here* >>

4. Name of applicant and official address
<< *Please enter information here* >>

5. Name of manufacturer of finished product and official address
<< *Please enter information here* >>

6. Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver solubility and dissolution studies were conducted
<< *Please enter information here* >>

I, the undersigned, certify, that the information provided in this application and the attached documents is correct and true

Signed on behalf of
<company>

_____ (Date)

_____ (Name and title)

1. Justification for a Biopharmaceutics Classification System (BCS) Biowaiver

1.1. Active Pharmaceutical Ingredient (API) Please confirm that the proposed product contains the same active substance (e.g. salt, ester, ether, isomer) as the comparator.
<< *Please enter information here* >>

1.2. Therapeutic Index of the API Please enclose a copy of the comparator product labelling and literature references employed to support that the drug does not exhibit a narrow therapeutic index for all authorised indications
<< *Please enter information here* >>

1.3. Pharmacokinetic properties of the API Please enclose a copy of the literature references employed to document the PK properties (PK linearity or reasons for non-linearity).
<< *Please enter information here* >>

1.4. Dosage form Please confirm that: • the dosage form is an immediate release product for systemic action • the posology is limited to oral administration • the administration without water is not included in the proposed posology
<< *Please enter information here* >>

1.0 COMMENTS FROM REVIEW OF SECTION 1 – BO*MRA USE ONLY*

2. Solubility

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the WHO PQTm document *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.)

2.1. Maximum therapeutic dose of the API Please enclose a copy of the labelling of the comparator product to document the maximum single dose that can be administered in a single administration (e.g. two tablets together).
<< *Please enter information here* >>

2.2. Stability of the drug in the physiological pH range Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract. Please discuss the ability of the analytical method to distinguish the API from its degradation products.
<< *Please enter information here* >>

2.3. Method of solubility determination Please describe method and conditions (e.g. shake flask method at 37±1°C) Please indicate also location of the solubility study protocol.
<< *Please enter information here* >>

2.4. Solubility study dates Please indicate dates of study protocol, study conductance and study report
<< *Please enter information here* >>

2.5. Analytical method validation Please summarise the results and indicate location in the documentation.
<< *Please enter information here* >>

2.6. Results

Please indicate location of the solubility study report.
Please fill in the following table for the necessary pH values. Add as many rows as necessary to create a solubility – pH profile

Theoretical pH	Observed pH	Adjusted pH	Individual concentration at saturation (Cs) values	Cs (mean and CV(%))	Amount that can be dissolved in 250 mL
pH 1.2	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermdiate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 4.5	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 6.8	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Other intermediate pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		

2.7. Plot the Solubility – pH profile

Please attach the plot of the pH-solubility profile based on the above data

<< Please enter information here >>

2.0 COMMENTS FROM REVIEW OF SECTION 2 – BOMRA *USE ONLY*

3. Absorption / Permeability

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the WHO PQTm document *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.)

3.1. Target Animal Species mass balance studies Summarise results of all studies found in the literature. Please enclose a copy of the references describing target animal species mass balance studies of the API.
<< *Please enter information here* >>

3.2. Target Animal Species absolute bioavailability studies Summarise results of all studies found in the literature. Please enclose a copy of the references describing target animal species absolute bioavailability of the API.
<< *Please enter information here* >>

3.3. Supportive studies Summarise results of all studies found in the literature regarding in vivo or in situ intestinal perfusion animal models or in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) with a positive and negative control. Please enclose a copy of the references.
<< *Please enter information here* >>

3.0 COMMENTS FROM REVIEW OF SECTION 3 – BO*MRA USE ONLY*

4. Test product

4.1 Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

- Please state the location of the master formulae in the quality part of the submission.
- Tabulate the composition of each product strength using the table below.
- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating/hard capsule, if any.
- Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

Please note: If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used

Composition of the batches used for comparative dissolution studies				
Batch number				
Batch size (number of unit doses)				
Date of manufacture				
Comments, if any				
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)				
Ingredients (Quality standard)	**Unit dose (mg)**	**Unit dose (%)**	**Biobatch (kg)**	**Biobatch (%)**
Equivalence of the compositions or justified differences				

4.2 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 (CoA) in this biowaiver submission.

<< Please enter information here >>

4.0 COMMENTS FROM REVIEW OF SECTION 4 – BO*MRA USE ONLY*

5. Comparator product

5.1. Comparator product Please indicate location in the documentation of the following documents that should be enclosed: A copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate. A copy of the comparator product carton outer box. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling. This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.
<< *Please enter information here* >>

5.2. Name and manufacturer of the comparator product and official address
<< *Please enter information here* >>

5.3. Qualitative (and quantitative, if available) information on the composition of the comparator product Please tabulate the composition of the comparator product based on available information and state the source of this information.

Composition of the comparator product used in dissolution studies		
Batch number		
Expiry date		
Comments, if any		
Ingredients	**Unit dose (mg)**	**Unit dose (%)**

5.4. Identify the source of the comparator product (where it was purchased), the method of shipment, and storage conditions of the comparator product from the time of purchase until completion of the comparative dissolution studies.

Please attach relevant copies of the following documents proving the stated conditions:
A copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.

<< *Please enter information here* >>

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

This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.

<< *Please enter information here* >>

5.0 COMMENTS FROM REVIEW OF SECTION 5 – BOMRA *USE ONLY*

6. Comparison of test and comparator formulations

6.1. Identify any excipients present in either product that are known to impact *in vivo* absorption processes A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.
<< *Please enter information here* >>

6.2. Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.
<< *Please enter information here* >>

6.3. Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption
<< *Please enter information here* >>

6.0 COMMENTS FROM REVIEW OF SECTION 6 – BO*MRA USE ONLY*

7. Comparative in vitro dissolution

7.1. Comparative in vitro dissolution

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
Please state the location of:

- the dissolution study protocol(s) in this biowaiver application
- the dissolution study report(s) in this biowaiver application
- the analytical method validation report in this biowaiver application

<< *Please enter information here* >>

7.2. Dissolution study dates

Please indicate dates of study protocol, study conductance and study report

<< *Please enter information here* >>

7.3. Summary of the dissolution conditions and method described in the study report(s)

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, filtration and storage. Deviations from the sampling protocol should also be reported.

7.3.1. Dissolution media: Composition, temperature, volume, and method of de-aeration

<< *Please enter information here* >>

7.3.2. Type of apparatus and agitation speed(s) employed

<< *Please enter information here* >>

7.3.3. Number of units employed

<< *Please enter information here* >>

7.3.4. Sample collection: method of collection, sampling times, sample handling, filtration and storage
<< *Please enter information here* >>

7.3.5. Deviations from sampling protocol
<< *Please enter information here* >>

7.4. Summarize the results of the dissolution study(s) Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.
<< *Please enter information here* >>

7.5. Summarize conclusions taken from dissolution study(s) Please provide a summary statement of the studies performed.
<< *Please enter information here* >>

7.6. Dissolution specifications Please provide proposed dissolution specifications and discuss them in relation to the results obtained in the BCS biowaiver.
<< *Please enter information here* >>

7.0 COMMENTS FROM REVIEW OF SECTION 7 – BO*MRA USE ONLY*

8. Quality assurance

8.1. Internal quality assurance methods

Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.

<< *Please enter information here* >>

8.2. Auditing and inspections

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.

<< *Please enter information here* >>

8.0 COMMENTS FROM REVIEW OF SECTION 8 – BO*MRA USE ONLY*

CONCLUSIONS AND RECOMMENDATIONS – BO*MRA USE ONLY*