CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205598Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(This Recommendation includes the Manufacturing Facilities Inspection Recommendation)

NDA 205598
Review #2
Review Date (see last page)

Drug Name/Dosage Form	Macimorelin granules for oral solution
Strength	60 mg to be reconstituted in 120 mL of water
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Aeterna Zentaris

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	11/5/13
0010	4/22/14
0013	6/26/14
0021	8/26/14
0031	6/30/17
0032	7/3/17
0034	8/3/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Team Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Martin Haber /Donna Christner	New Drug API/ONDP
Drug Product	Martin Haber/Christopher Galliford/Danae Christodoulou	ONDQA and New Drug Products II/ONDP
Facility	Laurie Nelson/Juandria Williams	Inspectional Assessment/OPF
Biopharmaceutics	Assadollah Noory/Tapash Ghosh/ Suneet Shukla/Haritha Mandula	ONDQA and Biopharmaceutics/ONDP

Executive Summary

I. Recommendation and Conclusion on Approvability

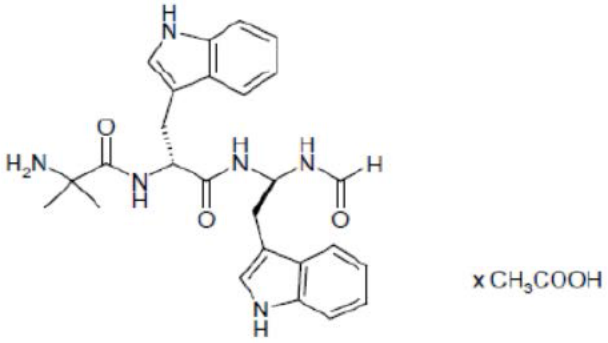
The OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

[Note: The labeling information in this OPQ review is not considered final because this specific work is currently ongoing as part of the OND-managed interdisciplinary labeling review. The final labeling will be part of the OND's action letter.]

II. Summary of Quality Assessment

NDA 205598 is a 505(b)(1) application for macimorelin, a New Molecular Entity (see Attachment B for details).

D-Tryptophanamide, 2-methylalanyl-N-[(1R)-1-(formylamino)-2-(1H-indol-3-yl)ethyl]-acetate



x CH_3COOH

$C_{26}H_{30}N_6O_3$ x $C_2H_4O_2$
Mol. Weight: 474.5 g/mol (base); 535.6 g/mole (acetate salt)

The drug substance is macimorelin acetate, a small synthetic peptide consisting of two D-tryptophan residues and one amino isobutyric acid group, manufactured by (b) (4). Solubility in the pH range 1-8 is approximately 300 mg/mL. The drug substance specification is standard for a small synthetic molecule and includes the following attributes: macimorelin identity (HPLC, NMR and optical rotation), acetate identity (HPLC), residual solvents, water content, sulphated ash, heavy metals, related substances (specified, unidentified, and total), chiral purity, macimorelin assay (HPLC), acetate assay, and microbial tests. Sufficient drug substance stability information is provided to support the retest period of (b) (4) months at (b) (4)°C.

The drug product is 60 mg macimorelin (or (b) (4) mg of macimorelin acetate,) formulated as granules and packaged in (b) (4) to be reconstituted in 120 mL of water to a final concentration of 0.5 mg/mL oral solution. The (b) (4)% overfill (i.e., each (b) (4) contains a total of (b) (4) mg macimorelin) is adequate (b) (4) Excipients are lactose monohydrate, crospovidone, colloidal silicon dioxide, sodium stearyl

fumarate and saccharin sodium [(b) (4)] all are compendial. The manufacturing process involves [(b) (4)] [(b) (4)] The drug product specification is standard for the dosage form: identity (HPLC and UV), average filling quantity, assay (HPLC), uniformity of dosage units, degradants (specified, unidentified, and total), concentration after reconstitution, and microbial tests. The expiration dating period is 48 months at 2-8 °C. After reconstitution in water, the oral solution is for immediate use (i.e., no in-use storage).

NDA 205598 was submitted on 11/5/2013 and received a Complete Response due to clinical deficiencies. The ONDQA CMC review #1 and Biopharmaceutics review from the first review cycle (Attachments A-C) recommended "approval" at the time of the action with no pending CMC issue.

The resubmission dated 6/30/2017 includes the following Quality information (found adequate by the OPQ team in this OPQ review #2, including OPF/DIA's re-evaluation of manufacturing/testing/packaging facilities):

- API: Updated information in the manufacturing process to include critical process parameters, process validation results, identification of an impurity that was previously unidentified [(b) (4)] now identified as [(b) (4)]), batch data for a process validation batch (MZ77337), additional stability data to support a retest period of [(b) (4)] months at [(b) (4)] °C, and solubility data.
- DRUG PRODUCT: Process validation results, tightening of the limit on impurity [(b) (4)] from [(b) (4)]% to [(b) (4)]%, batch data for a process validation batch (4001V) that was also used as the clinical batch in the resubmission, additional stability data, and a risk assessment for elemental impurities. The additional stability data support the final expiration dating period of 48 months when stored at 2-8 °C.

Suong T. Tran -S

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Suong (Su) Tran, Ph.D., OPQ ATL
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CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chaper II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Attachments:

A. Biopharmaceutics review dated 6/17/14
B. Quality review #1 dated 7/3/14
C. Quality addendum dated 9/15/14

CHAPTER I: Drug Substance

Additional information is in Attachment B and C

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Martin Haber

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Donna Christner

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CHAPTER II: Drug Product

Additional information is in Attachment B and C

NDA 205598

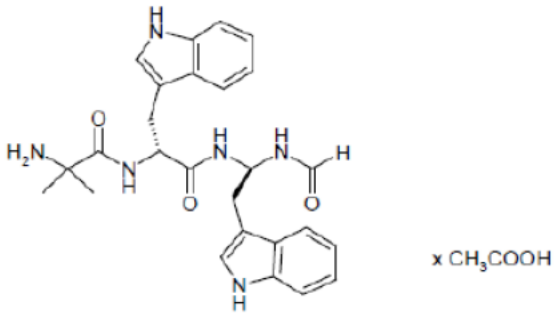
Introduction:
NDA 205598 for Macrilen™ (Macimorelin Acetate) was originally submitted to the Division of Metabolism and Endocrinology Products on 11/05/2013. The active pharmaceutical ingredient is the NME macimorelin acetate, a ghrelin receptor agonist with growth hormone secretagogue activity. It contains three amino acid derivatives in a single chain, two stereogenic centers and two peptide bonds. The drug product dosage form is [redacted] (b) (4), for reconstitution into an oral solution. The drug product is contained in an aluminum [redacted] (b) (4) pouch.

The CMC information provided for both drug substance and drug product in the application in conjunction with two amendments provided later in the review cycle were reviewed by Martin Haber PhD and found to be adequate on 07/03/2014. Subsequently, a recommendation for approval from a CMC perspective was made. Furthermore, as requested by the agency, the applicant subsequently elucidated the structure of '[redacted] (b) (4)' and this information was also found to be adequate on 09/15/2014.

However, during the review cycle, a significant drug-related safety issue identified, and the drug was not approved pending further clinical evaluation of the drug's safety by the sponsor. A complete response was recommended on 11/05/2014. After completing further clinical studies outlined in the complete response, the sponsor has resubmitted Macrilen™ (Macimorelin Acetate) to the division with a status date of 06/30/2017 with additional CMC information which will be the subject of this review.

Macrilen™ (USAN: Macimorelin Acetate, CAS 945212-59-9):

D-Tryptophanamide, 2-methylalanyl-N-[(1R)-1-(formylamino)-2-(1H-indol-3-yl)ethyl]-acetate



$C_{26}H_{30}N_6O_3$ x $C_2H_4O_2$
Mol. Weight: 474.5 g/mol (base); 535.6 g/mole (acetate salt)

Summary of Changes:
The applicant has provided a summary of changes with the updated submission. The most significant of these changes are described below:

- *A new clinical lot 4001V was manufactured and used to support new clinical studies and stability.*
- *Additional in process controls have been implemented.*
- *The stability program for validation batches has been modified.*

These changes are discussed in more detail below:

New Clinical Batch 4001V:

A summary of the batch analysis results for the previous lots and new batch 4001V that is reproduced below. In terms of quality, the batches are comparable with batch 4001V being representative of the product intended for marketing.

Table 1: Batch overview

Batch no.	Batch size	Date of manufacture	API per (b) (4)	Target filling weight	API batch used for manufacture	Use
D10024	(b) (4)	02/2010	(b) (4)	(b) (4)	MZ77061	S, C
C1110002		10/2011	60 mg		MZ77179	S, C
C1110003		10/2011	60 mg		MZ77179	S
C1110004		10/2011	60 mg		MZ77172 MZ77179	S
C1209006		09/2012	(b) (4)	1817 mg	MZ77239	-
4001V		07/2014		1817 mg	MZ77241	V, S, C

C = clinical trials, S = stability, V = validation

Table 2: Batch analyses results

Test parameter	Specification	Batch no.					
		D10024	C1110002	C1110003	C1110004	C1209006	4001V
Description	White to off-white granules in aluminum foil (b) (4)	conforms	conforms	conforms	conforms	conforms	conforms
Identity of macimorelin (HPLC)	Comparable retention times (± (b) (4) min) of peaks in test and reference solution	conforms	conforms	conforms	conforms	conforms	conforms
Identity of macimorelin (UV)	Comparable shape and position of absorption bands in test and reference solution	conforms	conforms	conforms	conforms	conforms	n.a. [5]
Average filling quantity [mg]	(b) (4)						(b) (4)
(b) (4) [%]							
Unidentified degradation product, RRT (b) (4) [%]							
Unidentified degradation product, RRT (b) (4) [%]							
Unidentified degradation product, RRT (b) (4) %]							
Unidentified degradation product, RRT (b) (4) %]							
Unidentified degradation product, RRT (b) (4) %]							

Test parameter	Specification	Batch no.					
		D10024	C1110002	C1110003	C1110004	C1209006	4001V
Total sum of degradation products [%]	(b) (4)						
Average content of macimorelin [%]							
Content uniformity							
Average concentration of macimorelin in drinking solution [mg/ml]							
TAMC [CFU/g]							
TYMC [CFU/g]							
Absence of E. coli (1 g)	absent	absent	absent	absent	absent	n.a.	absent
Testing procedure used for analyses		TP_0824_01		TP_0882_03		TP_0882_04	TP_0971_02
(b) (4)							

LOQ = limit of quantitation
n.a. = not analysed
n.c. = not calculabe
n.d. = not detectable

Adequate.

In Process Controls

The in process controls for the critical quality attributes are reproduced from the application here:

Table 1: In-process-controls

IPC	Specification
(b) (4)	

(b) (4)

Stability Data:
The application contains 48 months of stability data from lots D10024, C1110003, C1110004 and C1110002 which adequately support the requested shelf life of 48 months when stored at 2-8 °C. An additional 24 months of stability data for batch 4001V has also been included in the resubmission. There are no identifiable trends in impurities between the prior batches and batch 4001V and in particular, the levels of the degradation impurity (b) (4) are almost identical.

The sponsor has committed to continuing the ongoing stability study for the validation batch 4001V for s minimum of 48 months. The study will be performed by Allphamed Pharbil (including sample storage and sample analyses) and comprises two storage conditions (2-8 °C and 25 °C/60% r.h.). Samples at 2-8 °C will be stored for at least 48 months, samples at 25 °C/60% r.h. will be stored for at least 6 months. In addition, at least one commercial batch per year will be put on stability at the intended storage conditions of 2-8 °C. An annual retest up to the end of shelf-life will be performed according to the current testing procedure and shelf-life specification.

A photostability study was reported in the original submission. Samples were exposed to 1.2 million lux hours of light. Exposure to light led to formation of various individual degradation products (at least 24 products characterized by RRT were detected). The light exposed sample showed a degradation of about (b) (4) compared to the dark control. Macimorelin drug substance is regarded as photosensitive, but when stored in the aluminum foil presentation, no photodegradation is observed.
Adequate.

Labeling & Package Insert
Carton Labels:

APPEARS THIS WAY ON ORIGINAL

Package Insert:

- Dosage Forms and Strengths

As in the previous submission the PI states "(b) (4) "
Adequate.

- Description

Structure and name of the excipients are provided.
Adequate.

- How Supplied/Storage and Handling

PI states "Macrilen is supplied as off-white granules in an aluminum pouch. Each pouch contains (b) (4) that when reconsitituted with 120 mL of water provides (b) (4) ."
Adequate.

Environmental Assessment Or Claim Of Categorical Exclusion

The sponsor requests a categorical exclusion from submitting an Environmental Assessment based on the calculated estimated introduction concentration into the aquatic environment. The estimated introduction

concentration (EIC) into the aquatic environment was calculated to be (b) (4) ppb. This value is well below the threshold of 1 ppb which would require an environmental assessment. Therefore, the claim of categorical exclusion can be granted.

Christopher Galliford

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Danae Christodoulou

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CHAPTER III: Environmental Analysis

See chapter II

CHAPTER IV: Labeling

See chapter II

CHAPTER V: Process

See chapter II and Attachment B

CHAPTER VI: Facilities

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Juandria Williams

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CHAPTER VII: Biopharmaceutics

See Attachment A

CHAPTER VIII: Microbiology

Not applicable

ATTACHMENTS

A. Biopharmaceutics review dated 6/17/14
B. Quality review #1 dated 7/3/14
C. Quality addendum dated 9/15/14

ATTACHMENT A

From the first review cycle:
6/17/2014 ONDQA Biopharmaceutics

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-598	**Reviewer:** Assadollah Noory, Ph.D.	
Receipt Date:	November 5, 2013,		
Division:	Division of Metabolic and Endocrine Drug Products	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Aeterna Zentaris (AEZS)	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	MACRILEN®	**Date Assigned:**	February 25, 2014
Established Name:	Macimorelin acetate	**Date of Review:**	March 26, 2014
Indication:	Diagnosis of adult growth hormone deficiency (AGHD)	**Type of Submission:** Original New Drug Application – 505(b)(1)	
Dosage form/ strengths	Granules for Oral Solution		
Route of Administration	Oral		
Type of Review:	Biowaiver Request		

Aeterna Zentaris submitted this NDA for the approval of macimorelin acetate (MACRILEN) granules for oral solution for the diagnosis of adult growth hormone deficiency (AGHD) (b) (4) [redacted] Macimorelin acetate is a new molecular entity (NME). This NME has Orphan Designation, OD# 06-2255 and the indication is covered within the granted orphan designation. Macimorelin, a single dose product, will be provided as granules in an aluminum foil (b) (4) [redacted] Prior to administration to the patient, the granules will be dissolved in water. An aliquot of this prepared solution will be administered orally at the dose of 0.5 mg/kg bodyweight at the time that the diagnostic test is to be performed.

Background:
At the pre-NDA meeting, the Agency pointed out that the Sponsor could request a biowaiver for the to-be-marketed product during submission of the NDA, provided that the sponsor submits data to support the bridging of the different formulations using the solubilization methodology under various conditions of stirring and time. The information must include: A complete qualitative and quantitative composition of all formulations used in the clinical studies, and the to-be-marketed drug product supporting the similarity of these formulations, and the effect of stirring speeds on the dissolution upon reconstitution under various conditions like temperature (room temperature, cold and hot) and various agitation of the macimorelin solution.

Drug Product and Formulation:
Macimorelin acetate was synthesized by AEZS in its own research labs. It was then out-licensed it to

Ardana Bioscience, Edinburgh, U.K. in 2004. In the early stages of clinical development Ardana used API dissolved in water or acidified water to administer the dose. Ardana then contracted development of a formulation through (b) (4)
Process development at (b) (4) was aimed at finding a formulation which could be filled into (b) (4)
During the development of (b) (4), the Phase III study (ARD-0705-001) was initiated by Ardana; however, the (b) (4) was not available on time for the clinical study. In the year 2009 Aeterna Zentaris re-acquired the product; upon resuming, AEZS decided to utilize the existing formulation with minor modification and the Phase III study MACRILEN-047 was then completed with the modified formulation. AEZS manufactured additional batches; the composition of the formulation remained unchanged but (b) (4).

The general properties of Macimorelin acetate is shown in the following table.

Description	Off-white to pale yellow powder
Chirality	Macimorelin has two chiral centers in D,D (R,R) configuration
Molecular formula	$C_{26}H_{30}N_6O_3 \times C_2H_4O_2$
Molecular weight	474.5 g/mol (base); 535.6 g/mole (acetate salt)
pH-value (1% aqueous solution)	6.1
Solubility [a)]	Water: 300 g/l (pH 1 – pH 8) Ethanol: 260 g/l Acetonitrile: 40 g/l
Polymorphism	Not applicable as macimorelin acetate is amorphous
Hygroscopicity	Macimorelin acetate is hygroscopic

a) Refers to macimorelin base.

The formulation compositions are shown in the following table. Of note, AEZS (b) (4) will not possibly affect the bioavailability of this oral solution. The major difference between the AEZS' clinical formulation and Ardana's is the (b) (4), which was later adjusted to be same as Ardana's formulation for the to-be-marketed product for the convenience of dose administration of mL/Kg bodyweight (table below).

Table 4: Comparison of compositions

	Ardana clinically-tested formulation		AEZS clinically-tested formulation		AEZS to-be-marketed formulation (b) (4) overfill)	
Raw Material	**Unit quantity[a]**	**Centesimal Quantity**	**Unit quantity**	**Centesimal Quantity**	**Unit quantity**	**Centesimal Quantity**
Macimorelin (as acetate)	50 mg [b]	(b) (4)	(b) (4)		(b) (4)	
Lactose monohydrate (b) (4) (b) (4)						
Crospovidone (b) (4)						
Saccharin sodium						
Colloidal silicon dioxide						
Sodium stearyl fumarate						
Total		**100.0%**	(b) (4)	**100.0%**	**1817 mg**	**100.0%**
Volume of water for reconstitution	**100 mL**				**120 mL**	

[a]: API and excipients provided in separate containers

[b]: refers to macimorelin base

(b) (4)

The to-be-marketed formulation is (b) (4) to the AEZS-clinically-tested formulation. When the content is dissolved in 120 mL of water; the resulting solution has a concentration of (b) (4) mg/mL which facilitates dosing administration of 0.5 mg/Kg body weight. The (b) (4) mg/mL is by design (b) (4). The similarity in the formulation composition among the three formulations shown above provides a bridge between these formulations.

Solubilization characteristics:

The effect of temperature on the solubility of macimorelin acetate granules were carried out. Magnetic stirrer at 500 rpm stirring speed was used; the temperatures of the solutions were at 15°C, 22°C, and30°C. The summary results are shown in the following table.

Influence Of Water Temperature At 500 RPM, Mean (RSD)			
Formulation	**water temperature**		
	15°C	**22°C**	**30°C**
Ardana- clinical	99.2 (0.7%)	101.3 (0.7%)	98.2 (3.8%)
AEZS-clinical	92.3 (1.4%)	87.6 (1.0%)	86.2 (1.0%)
To-be-marketed	98.5 (2.4%)	95.7 (1.8%)	93.3 (1.8%)

The results indicate that there was no significant difference in the solubility of different formulations due to temperatures, especially between the Ardana-clinical and to-be-marketed formulations.

The following table and figure show the result of solubility of macimorelin acetate granules at room temperature *with no agitation* to the solution.

Table 16: Solubilized API (mean) in an unstirred solution, data normalized to a start value of 100%

		Solubilized API [%]				
		after 0 min	after 10 min	after 15 min	after 20 min	after 30 min
Ardana clinically-tested formulation	Mean	100.0	99.8	99.5	99.3	99.2
	RSD	1.2	1.4	1.4	1.3	1.2
AEZS clinically-tested formulation	Mean	100.0	98.8	98.5	98.0	97.6
	RSD	1.4	1.1	1.0	1.0	1.1
AEZS to-be-marketed formulation	Mean	100.0	98.4	97.9	97.5	96.8
	RSD	2.0	1.8	1.9	1.8	1.8

The data indicate that the solubility of the formulations are similar at room temperature without any agitation of the solution.

The effect of agitation on the solubility of macimorelin acetate granules were carried out at **22°C**. Magnetic stirrer at 250 rpm, 500 rpm, and 750 rpm stirring speed was used to determine the solubility of macimorelin acetate granules. The summary results are shown in the following table.

Influence Of Stirring Speed At 22°C, Mean (RSD)			
Formulation	**Stirring Speed**		
	250	**500**	**750**
AEZS-clinical	88.6 (0.9%)	87.6 (1.0%)	89.0 ((b) (4)
To-be-marketed	96.8 (1.0%)	95.7 (1.8%)	97.8 (1.7%)

The results indicate that there was no significant difference in the solubility of macimorelin acetate granules from AEZS-clinical and to-be-marketed formulations due to different agitation speeds.

In summary, based on the solubility profiles observed from the various products under various temperatures and agitations, it appears that the (b) (4) the AEZS-formulations is not expected to influence the bioavailability of macimorelin. Therefore a waiver from conducting an in-vivo bioavailability study for NDA 205598 is granted from biopharmaceutics perspective.

RECOMMENDATION:

The Office of New Drug Quality Assessment Completed the review of Biopharmaceutics portion of NDA 205-598 and recommends an approval with granting a bio-waiver for the AEZS-formulations.

Signature
Assadollah Noory, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Team Leader
Office of New Drug Quality Assessment

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/s/

ASSADOLLAH NOORY
06/17/2014

TAPASH K GHOSH
06/17/2014

ATTACHMENT B

From the first review cycle:
7/3/2014 ONDQA CMC review #1

NDA 205-598

Macrilen (macimorelin acetate) (b) (4) Oral Solution

Aeterna Zentaris GmbH

Martin Haber, Ph.D.
Division of New Drug Quality Assessment III

For
Division of Metabolism and Endocrinology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 205-598

2. REVIEW #1

3. REVIEW DATE: July 3, 2014

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	11/4/2013
Amendment	2/14/2014
Amendment	4/22/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Aeterna Zentaris
Address:	100 Marketplace Suite 203, 25 Mountainview Blvd, Basking Ridge, NJ 07920
Representative:	Nicholas J. Pelliccione, Ph.D.
Telephone:	908-626-5506

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Macrilen
b) Non-Proprietary Name (USAN):macimorelin acetate

c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Diagnosis agent

11. DOSAGE FORM: (b) (4) oral solution

12. STRENGTH/POTENCY: 60 mg (b) (4)

13. ROUTE OF ADMINISTRATION: Oral

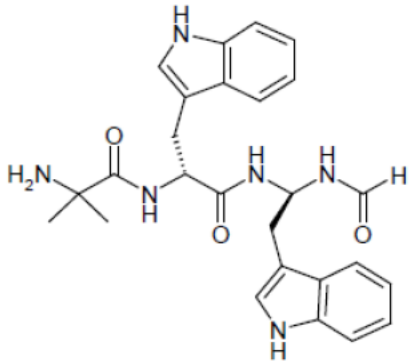
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

D-Tryptophanamide, 2-methylalanyl-N-[(1R)-1-(formylamino)-2-(1H-indol-3-yl)ethyl]-acetate



x CH_3COOH

$C_{26}H_{30}N_6O_3$ x $C_2H_4O_2$
Mol. Weight: 474.5 g/mol (base); 535.6 g/mole (acetate salt)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: **Note: No DMF's were referenced. Sufficient information is in application.**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73196	Clinical trials

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Approval	6/5/2014	Jeffrey Quinn, PhD
Biopharm	Approval	6/17/2014	Assadollah Noory, PhD
Methods Validation	Not necessary		Part of this review
EA	Exclusion requested and accepted		Part of this review
Microbiology	Approval	11/6/2013	Bryan Riley, PhD

The Chemistry Review for NDA 205-598

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval, pending satisfactory evaluation of the cGMP status of the manufacturing facilities by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, macimorelin acetate, is a ghrelin receptor agonist with growth hormone secretagogue activity. It contains three amino acid derivatives in a single chain, two chiral centers and two peptide bonds. The drug substance is manufactured by (b) (4) and the key intermediate is manufactured by (b) (4) Macimorelin acetate is manufactured by (b) (4). The chemical structure was confirmed by several chemical methods including NMR and mass spectroscopy. Two organic impurities were detected in the drug substance, (b) (4) and unidentified (b) (4) The sponsor is working to identify (b) (4) There are four stereo isomers of macimorelin due to the two chiral centers, macimorelin is the D,D (R,R) isomer. The drug substance specifications include the following release tests for macimorelin: identity (HPLC, NMR and optical rotation), acetate identity (HPLC), residual solvents (b) (4), water content, sulphated ash, heavy metals, related substances (specified impurities (b) (4) each unidentified impurity and total sum of impurities), chiral purity, macimorelin assay (HPLC), acetate assay and microbial tests. Methods are described and validated. Batch release results are provided. Specifications were met and are acceptable. Drug substance stability data is provided to support storage at (b) (4) °C.

The drug product dosage form is (b) (4), for reconstitution into an oral solution. The drug product is contained in an aluminum (b) (4) pouch. There is one strength, (b) (4) mg macimorelin base, in the form of the acetate salt. This includes a (b) (4) overfill to (b) (4). The pouch formulation also contains the following excipients: (b) (4) mg lactose monohydrate, (b) (4)

mg crospovidone, (b) (4) mg colloidal silicon dioxide, (b) (4) mg sodium stearyl fumarate and (b) (4) mg saccharin sodium, (b) (4) The drug product is manufactured by Allphamed Pharbil GmbH, Germany. The manufacturing process (b) (4) All excipients are compendial. Drug product release tests include identity (HPLC and UV), average filling quantity, assay (HPLC), uniformity of dosage units, concentration after reconstitution and microbial tests. (b) (4) drug product release specifications include a limit for (b) (4) The sponsor agreed to tighten the shelf-life limit for (b) (4) to the release limit as no impurity was detected on stability at 2-8°C. The analytical methods were described and validated. Batch release test data is provided and specifications were met. Stability data is provided and an expiry of (b) (4) months for storage at 2-8°C is supported by the data.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the diagnosis of adult growth hormone deficiency (AGHD) (b) (4) The dose is calculated based on the patient's body weight, that is, 0.5 mg/Kg body weight. The content of one (b) (4) is dissolved in 120 mL of water by the health care provider. This forms a solution with a concentration of 0.5 mg/mL of macimorelin acetate. The solution is prepared in a suitable glass container with stirring for 2-3 minutes and should be used within 30 minutes after preparation. The calculated amount of solution based on the patient's body weight is administered orally.

C. Basis for Approvability or Not-Approval Recommendation

Macimorelin (b) (4) Oral Solution is a low risk product from CMC perspective. The drug substance is a well characterized tripeptide derivative and the drug product is a (b) (4) (granules) manufactured by (b) (4). The product is intended for one-time use after reconstitution in water. Microbiology and Quality Biopharmaceutical reviews recommend approval. A waiver is granted for different developmental formulations since the drug is dissolved in water before oral administration.

III. Administrative

A. Reviewer's Signature

See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

See DARRTS

72 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN T HABER
07/03/2014

DANAE D CHRISTODOULOU
07/03/2014
I concur with the reviewer's conclusion and recommendation

ATTACHMENT C

From the first review cycle:
9/15/2014 ONDQA review addendum

Memorandum

Date: September 15, 2014

From: Martin Haber, Ph.D., Review Chemist

Subject: NDA 205598 Structure of (b) (4) in macimorelin acetate

The applicant initially was unable to determine the structure of unidentified (b) (4) In an amendment dated 8/26/2014, they have determined the structure below (stereochemistry still undefined for new chiral centers) for (b) (4)

(b) (4)

(b) (4)

An (Q)SAR assessment of the structure with DEREK Nexus and MCase software indicated that (b) (4) is not mutagenic.

Conclusion: The applicant has identified (b) (4) as requested by the Agency. The overall chemistry, manufacturing and controls recommendation is unchanged and remains recommending approval, pending satisfactory evaluation of the cGMP status of the manufacturing facilities by the Office of Compliance.

R/D Init by: Dr. D. Christodoulou, Branch Chief

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN T HABER
09/15/2014

DANAE D CHRISTODOULOU
09/15/2014

Su (Suong) Tran

Digitally signed by Su (Suong) Tran
Date: 11/17/2017 08:26:46AM
GUID: 508da71f00029ec8b75e233f12b15339

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205598
2. DATES AND GOALS:

Letter Date: 04-NOV-2013	Submission Received Date : 05-NOV-2013
PDUFA Goal Date: 05-NOV-2014 (NDA in "The Program")	

3. PRODUCT PROPERTIES:

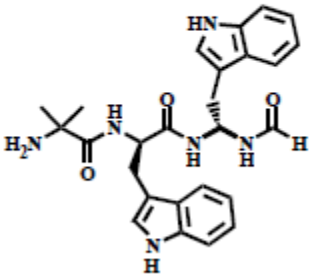
Trade or Proprietary Name:	Macrilen (proposed)
Established or Non-Proprietary Name (USAN):	Macimorelin acetate
Dosage Form:	(b) (4) oral solution
Route of Administration	Oral
Strength/Potency	0.5 mg/mL reconstituted solution (60 mg (b) (4))
Rx/OTC Dispensed:	Rx

4. INDICATION: Diagnosis of adult growth hormone deficiency
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Chemical name:

Amino isobutyryl-D-tryptophanyl-gem-diamino-D-tryptophanyl-formaldehyde, acetate salt

Structure:



Aib-D-Trp-D-gTrp-CHO

6. NAME OF APPLICANT (as indicated on Form 356h): Aeterna Zentaris GmbH

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	1
Application Type	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDPQ PM
Pharmacology/Toxicology	x		Review of impurity qualification information.
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment		x	Categorical exclusion request to be reviewed by Primary Reviewer
CDRH		x	
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes

CMC Comments for 74-Day Letter:

1. **We acknowledge your ongoing effort to identify (b) (4) in the drug substance. Provide the most current summary of past and current studies conducted in this investigation**
2. **We acknowledge that you followed our 13-DEC-2011 advice to include an overfill in the drug product packaging (b) (4) . However, the NDA does not include information on how the amount of (b) (4) was selected to be an adequate overfill to ensure the target concentration of 0.5 mg/mL macimorelin. Provide a rationale supported by data for the (b) (4) overfill. In addition, explain the impact on efficacy in a situation where the entire content of the (b) (4) including the (b) (4) overfill, can potentially be reconstituted resulting in a higher drug concentration than the target concentration.**
3. **Confirm that the 60 mg stability batches have the same formulation as the commercial**

product. Provide a revised table of formulations (e.g., Table 6 in 1.12.15, Table 2 in 2.3.P, Tablet 1 in 3.2.P.2) to include formulations used in clinical studies, stability studies, and commercial product. Revise the percentage quantities of ingredients in the commercial formulation because the current values in the NDA appear to be incorrect.

4. **Provide a justification for the omission of Water Content, pH, and Reconstitution Time in the drug product specification.**

Biopharmaceutics: not applicable

From: Ghosh, Tapash
Sent: Tuesday, November 05, 2013 11:21 AM
To: Tran, Suong T; Christodoulou, Danae D; Kumar, Priyanka
Cc: Ghosh, Tapash
Subject: RE: NEW NDA 205598 macimorelin acetate granules for oral solution

No biopharm review/er needed here. Thanks,

Microbiology: not applicable

From: CDER OPS IO MICRO
To: Tran, Suong T; Christodoulou, Danae D; Kumar, Priyanka; Ghosh, Tapash; CDER OPS IO MICRO
Subject: RE: NEW NDA 205598 macimorelin acetate granules for oral solution
Date: Wednesday, November 06, 2013 8:38:51 AM

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

Thanks, Vera

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	No because the drug product is for diagnostic use (one-time administration) and is not a complex dosage form ((b) (4) to be reconstituted in water for oral administration)

Summary of Critical Issues and Complexities

Initial Quality Assessment

Previous quality-related meeting between FDA and the sponsor:

Type C meeting minutes dated 13-DEC-2011:

8. The process for synthesizing this DS was validated in 2006 under the previous sponsor's direction. In the interim, minor modifications to the process have been made. These modifications affect the manufacture (b) (4) All other conditions and synthetic steps are unchanged. The resulting batches showed no changes in terms of physico- chemical properties, but did demonstrate an enhancement of the qualitative and quantitative impurity profile of the DS. Overall, we consider the changes to the manufacturing process to be minor. Whereas the modified and improved process for (b) (4) has been completely validated, we propose to re-validate the subsequent process steps using a concurrent validation approach.Prior to the completion of concurrent validation, we propose to use the batches in drug product for commercial distribution based on thorough monitoring and testing of the API batches.
Does the agency agree that these manufacturing changes can be classified as minor and that our proposal for validating the current process is acceptable?

FDA Response
FDA requires that drug manufacturers validate their manufacturing processes but does not prescribe how that is to be accomplished and does not approve process validation approaches, protocols, or specific batches used in process validation studies. Approaches to process validation will depend on multiple factors, some of which are specific to the complexity of the product and process. Process validation is evaluated during on-site inspections. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. Concurrent release may be considered for drug products with orphan drug status. Orphan drug status is recognized as a situation where, potentially, distribution of any given batch before completion of the initial process validation study may be justified for the greater public health benefit. With concurrent release, each process qualification batch is essentially released on its own merits without the assurance of quality conferred upon product made by a process proven to be consistent and reproducible, stable, and capable. Your criteria for batch release also will be reviewed. Please adhere to 21 CFR 211.165, Testing and Release for Distribution, which, in part, requires that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition of their approval and release. You may find more information on process validation and concurrent release in Guidance for Industry, Process Validation: General Principles and Practices (January 2011). http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

9. We intend the product to be labeled (b) (4), and that the product will be supplied in (b) (4) Investigations have shown that after preparation of the solution about (b) (4)% of the active ingredient is dissolved. Approximately (b) (4)% of the active remains in the (b) (4) (b) (4).
We believe that the amount of active administered is relevant for labeling, (b) (4).
Does the Agency agree that this will support a label statement of (b) (4)?

FDA Response
There are three issues concerning your proposal:
1. According to your estimates, approximately (b) (4)% of the active pharmaceutical ingredient (API) remains in the (b) (4) after transferring the contents from the (b) (4) into the liquid. Since typical drug product specifications for assay are (b) (4) % of the label claim, the potential exists or a patient to receive a dose approximately (b) (4)% of label claim ((b) (4) %). Therefore, the amount of active delivered with your current drug product is not within the normal limits of variation for this dosage form. As an alternative, manufacturers will sometimes include small amounts of "overfill" in drug product containers as a way to compensate for the portion of the product that may be lost when the drug is administered. Overfill is the volume or weight of the formulation filled in each container in slight excess of the labeled content. If an overfill is used, the amount of overfill in each container should be identified and the rationale for the amount of overfill should be provided.

2. From your description, it is unclear what the dosage form is for the drug. You propose to [redacted] See issue 3 below regarding the possibility of [redacted].

3. It is recommended that you reformulate your drug product to eliminate any potential dosing complication associated with [redacted]. Though you state that the patient will [redacted], the instructions for use do not support this statement: [redacted] Clarify this inconsistency. You should also provide information to support your claim [redacted] does not affect the efficacy. In addition, provide information (e.g., in vivo performance data)to support your statement "We believe the amount of active administered is relevant for labeling, [redacted]"

Also, provide detailed description and validation of the dissolution method including the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) as well as the data to support the discriminating capability of the selected method.

10. As discussed previously with the Agency (EOP2 meeting minutes dated July 9, 2007) there will be limited stability data, per ICH, available at the time of NDA submission. Data from one [redacted] batch ([redacted] of active ingredient) after 24 months and three [redacted] batches (containing 60mg of active ingredient), after 6 months will be submitted with the initial NDA. Additional studies conducted by Aeterna Zentaris on this formulation have indicated that storage at 2-8oC is required [redacted]. Storage at 2-8oC has shown acceptable impurity profiles up to 24 months thus far. The three additional batches of product in [redacted] will be manufactured at identical conditions to the ultimate commercial process, and at a scale that is comparable to the ultimate commercial scale ([redacted]% of full scale). It is our intention to provide updated stability data on these batches before completion of the NDA review period, as previously discussed by Ardana with the Agency. A suggested expiry will be identified based on the stability data available at the time of submission.

Does the Agency agree this plan for stability is acceptable?

FDA Response

We do not agree with your proposal to submit additional stability data during the NDA review cycle. You should include in the initial NDA submission all the stability data necessary for our review. Be advised that we will determine the shelf life of your product based on primary stability data as discussed in ICH Q1A(R2) Stability Testing of New Drug Substances and Products, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidan ces/UCM073369.pdf , and Q1E Evaluation of Stability Data http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073380.pdf. Our current policy regarding amendments submitted during theNDA review cycle is in accordance with the FDA's Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf, meaning that a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments.

11. Macimorelin for the diagnosis of adult growth hormone deficiency has been designated as an orphan drug, and thus we foresee a very limited demand for the product. We propose to design the Process Performance Qualification (PPQ) protocol to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e. concurrent release.

Does the agency find this proposal acceptable?

FDA Response

Please refer to the response to Question 8.

Type C meeting minutes dated 22-JUN-2012:

Aeterna Zentaris GmbH requested a Pre-New Drug Application (NDA) meeting with the Agency on March 19, 2012. This meeting was considered premature, however, the Agency did grant a Type C teleconference meeting to discuss drug development plans for IND 073196 (AEZS-130), specifically, Chemistry, Manufacturing and Controls (CMC), and clinical pharmacology issues. The Agency also agreed to send updated responses to clinical comments sent to the sponsor in a letter dated December 13, 2011.

DISCUSSION

Chemistry, Manufacturing and Controls (CMC)

The comments that issued to the sponsor on May 3, 2012, are repeated below in bold font, followed by the sponsor's response, emailed to the Agency on May 23, 2012, in italic font. A summary of the meeting discussion follows in bold italic font.

FDA Comment 1a
Due to the most recent change in the recommended administration of your drug product (b) (4) , the label "Macimorelin, Granules for Oral Solution" would be appropriate. However, the strength (in mg) should be representative of the amount of drug substance in solution following reconstitution of the drug product, (b) (4) . The labeling will also be required to state the drug concentration of the solution. This will provide a more accurate representation of the concentration of the drug substance after addition to water and subsequent dosing of the patient. In addition, the labeling will state the total amount of the drug substance present in each (b) (4) including the overfill amount.

AEZS Response 1a
The suggestions for revising the label to more accurately represent the amount of drug substance in solution are accepted. In order to make sure we understand correctly what will be expected in product label when submitting our NDA we would like the Division to consider the following proposed wording (understanding that this is ultimately a review issue):

(b) (4)

.

FDA Comment 1b
Propose a dosing conversion table (i.e., to convert milliliters of drug solution to the desired drug dose) to assist the healthcare provider in preparing an appropriate dose, which will be sufficient to assure efficacy of the drug product when administered as indicated.

AEZS Response 1b
By obtaining an effective concentration of 0.5 mg/ml macimorelin, the dosing of patients becomes straightforward. The dose to be administered is 0.5 mg macimorelin/kg body weight, therefore, at a concentration of 0.5 mg/ml the proper dose is 1 ml drug solution per kg body weight. We can supply examples in the package insert, for instance:
If the patient weighs 70 kg the correct dose to administer is 70 ml of the final drug solution.
If the patient weighs 92 kg the correct dose to administer is 92 ml of the final drug solution.
We believe this would be sufficient to ensure administration of the correct dose indicated.

FDA Comment 1c
Provide a detailed description and validation of the method used to measure the amount of Active Pharmaceutical Ingredient (API) in solution following addition of the drug product to the recommended volume of water.

AEZS Response 1c
The requested information regarding validation of the assay method for API in solution will be provided in the NDA.

Biopharmaceutics letter dated 04-MAR-2013:

Regarding the effect of concentration of the drug on absorption, does the proposed approach adequately address the Division's request for information?
FDA Response: Yes, your approach seems appropriate.

Question 2
Regarding composition and dissolution, does the proposed approach adequately address the Division's request for information?
FDA Response: No. Your proposed dissolution method is inappropriate for the given drug product. However, you may be able to bridge the different formulations (provided in Table 5 of your meeting package) using the solubilization methodology provided on Page 13 of the meeting package. To support the bridging of the three formulations provide the following comparison data using the solubilization methodology:
a. Collect solubility data using the above methodology by leaving the prepared solutions on the bench for additional time as per the following:
- With stirring for 2-3 minutes and collect sample for analysis
- Without stirring (and collect sample for analysis): 10 minutes, 15 minutes, 20 minutes and 30 minutes
b. Provide the non-normalized for target filling weight data for comparing the dosing solutions in addition to the data provided in Table 3.

Question 3
Regarding biowaiver requirements to evaluate the effects of various conditions and stirring speeds, does the proposed approach adequately address the Division's request for information?
FDA Response: No. As we stated in Response to Question 2, the proposed dissolution method is inappropriate for the given drug product (for e.g., (b) (4) is not suitable). Also note our request for additional data in our response for Question 2.

Question 4
Does the data and rationale presented herein support a request for a biowaiver to be submitted in a New Drug Application (NDA) for this product as a diagnostic for adult growth hormone deficiency?
FDA Response: Although the rationale provided comparing the composition of the three formulations appears appropriate and supports your request for a biowaiver, the data provided to support the approval of the biowaiver are not adequate. Please note that biowaivers are only granted during NDA review. Therefore, submit in your NDA submission the biowaiver request and supportive data noted in our response for Question 2.

Biopharmaceutics letter dated 20-MAR-2013:

Dissolution vs. Solubilization:
Regarding your comments on dissolution, AEZS mistakenly used the term 'dissolution' within the briefing document when it should have used the term 'solubilization'. In fact, all data in the briefing book except for table 4 were generated with the solubilization methodology provided on page 13 of the meeting package.
The data in Table 4 are meant to demonstrate that AEZS-130 adsorbed to excipients is released under physiological conditions with respect to pH and/or the composition of the medium in which it is dissolved. Inadvertently, (b) (4) , was mentioned on page 14 of the briefing APPEARS THIS WAY ON ORIGINAL book; however, the experiment was actually be conducted using a magnetic stirrer enabling higher rotation speeds (b) (4) (b) (4) which are necessary to keep the suspended particles from floating on the surface of the dissolution solvent.
Finally, as the drug product is administered as an oral solution, dissolution testing according to USP <711> is not applicable and it was not our intention to propose such a test.
It appears that our inadvertent use of the term 'dissolution' caused a misinterpretation of the results provided, but we believe our explanation clarifies this point.
FDA Response: Yes.

Question 2:
We appreciate the Agency's proposal for additional tests using the solubilization methodology. Using the basic methodology for solubilization as provided in our earlier submission, the studies will be conducted as follows:
Dissolve the (b) (4) by stirring for 2-3 minutes, take one sample immediately and further samples after

10, 15, 20 and 30 min from the same solution without stirring. This test will be performed with n=6 (b) (4) each from the clinically tested AEZS formulation, the AEZS to-be-marketed formulation and the Ardana clinically tested formulation.
Is our understanding of the proposed study design correct?
FDA Response: Please use n=12 sample size for each formulation. We agree with the rest of the proposal.

Question 3:
The effect of temperature and stirring speed on the solubilization procedure was presented in Appendices 3 & 4 of the briefing document. As explained above these data were not generated with a true 'dissolution method' as typically defined and therefore should fulfill the Division's request for information.
Does the Division agree?
FDA Response: Yes.

Drug Substance.

The drug substance is macimorelin acetate (USAN), a very small synthetic peptide (with 2 residues) and New Molecular Entity. The compound is amorphous and hygroscopic. The structure characterization was conducted with NMR (1H, 13C, 2D-EXSY, 2D-COSY), elemental analysis, IR, UV, and HPLC-MS. The two Trp groups are in the D configuration, the lack of racemization will be confirmed by the reviewer.

The manufacture is (b) (4). The current manufacturing process underwent revisions after 2006, and the comparability data (batch release and stability) will be evaluated by the reviewer to bridge the different batches.

The drug substance specification includes standard attributes for a small synthetic molecule (copied at the end of this review). The molecule chirality is controlled by optical rotation and capillary electrophoresis. There is a limit of (b) (4)% on water content. There are two specified impurities, (b) (4). Qualification of (b) (4) was conducted, and input from the Pharmacology Toxicology team will be obtained on the final limit. The (b) (4)% limit on (b) (4) does not require qualification but it should be identified per ICH guidelines. The applicant states that the identification work has not been successful (see 74-day letter comment). Based on available information in the NDA, the reviewer will determine whether the drug substance specification should include additional impurities.

The primary container closure system is a (b) (4) The drug substance is stored at (b) (4)°C. Primary stability data include two batches, MZ77179 (used in one clinical batch) and MZ77172, produced by the current manufacturing process and packaged in the proposed container closure system, with 24-month (b) (4) °C, 12-month (b) (4) and 6-month (b) (4). The NDA also includes photostability data and supportive stability data from batches manufactured by the previous process and that were used in toxicology studies.

Drug Product

The composition of the drug product is copied at the end of this review. There is no novel excipient. The drug product is packaged in a pouch/ (b) (4) with a target fill of 60 mg macimorelin (base). As previously discussed with FDA (see copied 13-DEC-2011 and 22-JUN-2012 meeting minutes), each (b) (4) has a (b) (4) overfill and contains (b) (4) mg macimorelin (base). (b) (4) to result in the final drug concentration of 0.5 mg/mL for oral administration. (b) (4)

(b) (4)

The use of an overfill was previously suggested to the applicant by FDA. However, the NDA does not include information on how the amount of (b) (4) was selected to be an adequate overfill to ensure the final concentration of 0.5 mg/mL macimorelin (see 74-day letter comment).

Comparability of the product used in the clinical studies, stability studies, and commercial product: The applicant states that clinical and stability batches were manufactured at commercial scale using the commercial process by the commercial manufacturer. The formulations are different for the clinical product and the commercial product as shown by the copied tablet below. It is noted that the formulation of the 60 mg stability batches is missing from the copied table and that the % quantity is incorrect for the commercial formulation (see 74-day letter comment).

- The NDA includes a biowaiver request regarding the bridging between the clinical formulation and the commercial formulation. The request includes permeability and absorption kinetics data and will be evaluated by the Clinical Pharmacology team.
- The primary stability batches appear to have the commercial formulation but without the (b) (4) overfill per (b) (4) (i.e., the primary stability batches have 60 mg macimorelin/ (b) (4) while the commercial product will have (b) (4) mg macimorelin/ (b) (4) Only one drug product batch with the overfill is reported in the NDA and only with batch release data.

Table 6: Comparison of composition

	Ardana clinically-tested formulation[a]		AEZS clinically-tested formulation[b]		AEZS to-be-marketed formulation (b) (4) overfill)	
Raw Material	**Unit quantity[c]**	**Centesimal Quantity**	**Unit quantity**	**Centesimal Quantity**	**Unit quantity**	**Centesimal Quantity**
Macimorelin (as acetate)	50 mg [d]	(b) (4)	(b) (4)			(b) (4)
Lactose monohydrate (b) (4)	(b) (4)					
(b) (4)						
Crospovidone (b) (4)						
Saccharin sodium						
Colloidal silicon dioxide						
Sodium stearyl fumarate						
Total		**100.0%**	(b) (4)	**100.0%**	**1817 mg**	**100.0%**
Volume of water for reconstitution	**100 mL**				**120 mL**	

[a]: In study AEZS-130-047, this formulation was administered to the 42 AGHD patients and the 10 matched controls enrolled in the first part of the study i.e., while the study was sponsored by Ardana.
[b]: In study AEZS-130-047, this formulation was administered to the 10 patients and 38 matched controls enrolled in the second part of the study i.e,, while the study was sponsored by Aeterna Zentaris.
[c]: API and excipients provided in separate containers.
[d]: Refers to macimorelin base.

(b) (4)

The drug product manufacture consists of (b) (4)

.

The drug product specification includes attributes standard for this type of dosage form ((b) (4) for reconstitution as oral solution) such as filling quantity, content uniformity, and reconstituted concentration. However, water content, pH, and reconstitution time are missing from the specification (see 74-day letter comment). The reconstitution time and associated test method are especially important because the directions for use state "2-3 minutes" as the time required to

dissolve the product in water; both the test method and acceptance criteria should support this labeling. In addition, (b) (4) both the reconstitution time and reconstituted concentration are important attributes, and their associated test methods should support the directions for use in the labeling. There is only one identified degradant, (b) (4) resulting from (b) (4). The limit of (b) (4)% on this degradant meets the ICH qualification threshold for the maximum daily dose of (b) (4) mg macimorelin. The limit of (b) (4)% on an unidentified degradant meets the ICH identification threshold.

The drug product is packaged in a 50 x 72 mm (b) (4) foil pouch/ (b) (4) There is no DMF referenced in the NDA for the (b) (4) components. Certificates from the manufacturer (b) (4)) are provided to state the identity of the (b) (4) components (from the product contact side outward: (b) (4) and that the components comply with FDA's indirect food additive regulations. Following FDA's guidance on containers/closures and internal policy, the reviewer will determine whether the provided information is sufficient for this type of dosage form ((b) (4) for reconstitution as oral solution). The applicant indicates that the stability batches were packaged in the commercial (b) (4)

Primary stability data are provided for three drug product batches manufactured at (b) (4) of the commercial scale using the commercial process(with the difference related to the (b) (4) overfill for the commercial product) at the commercial manufacturing site. As mentioned earlier in this review, the primary stability batches appear to have the commercial formulation (see 74-day letter comment) but without the (b) (4) overfill per (b) (4) (i.e., the primary stability batches have 60 mg macimorelin/ (b) (4) while the commercial product will have (b) (4) mg macimorelin/ (b) (4) Since the only difference is the (b) (4) overfill per (b) (4) the primary stability data are sufficient in determining the stability profile of the product and a shelf life. Primary stability data include three batches, C1110002 (clinical batch), C1110003, and C1110004, with 18-month at the long term 2-8 °C, 12-month at 30 °C/65% RH, and 6-month at 40°C/75% RH. The NDA also includes in-use data (to support the recommended use of the oral solution within 30 minutes after reconstitution) and supportive stability data one (b) (4) mg batch. It is noted that the data on the solution concentration (b) (4) in the proposed specification. (b) (4) (see earlier comments in this review) which eventually led to the (b) (4) overfill for the commercial product.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		

2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			

	Parameter	**Yes**	**No**	**Comment**
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?	x		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**

30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?			There is no DMF referenced in the NDA.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

This document will be electronically signed in DARRTS.

Appendix 1. Composition of Drug Product

One unit dose is contained in an aluminum (b) (4) consisting of 1817.2 mg granules for preparation of an oral solution. When the granules have been reconstituted in 120 mL of water, 1 mL provides 0.5 mg macimorelin. A bodyweight adjusted aliquot of the solution is administered to the patient.

Table 1: Composition per unit

Composition	Function	Standard	Mass / Sachet
Macimorelin (as acetate)	API	Internal	(b) (4)
Lactose monohydrate, (b) (4)	(b) (4)	USP-NF	
Crospovidone, (b) (4)		USP-NF	
Colloidal silicon dioxide		USP-NF	
Sodium stearyl fumarate		USP-NF	
Saccharin sodium, (b) (4)		USP-NF	
Total			1817.2 mg

a) Refers to macimorelin base
b) (b) (4)

Appendix 2. Drug Product Specification

Table 4: Release specification

Test no.	Description	Specification
1	**DESCRIPTION**	White to off-white granules in aluminum foil (b) (4)
2	**IDENTITY**	
2.1	**Macimorelin (HPLC)**	The peak of macimorelin in the solution to be tested and the peak of macimorelin in the reference solution for assay have to be comparable in retention time (tR ± 0.3 min).
2.2	**Macimorelin (UV)**	The UV spectrum of the peak corresponding to macimorelin in the test solution has to be comparable with regard to shape and position of absorption bands to that of the macimorelin peak in the reference solution.
3	**PROPERTIES AND PURITY**	
3.1	**Average filling quantity**	(b) (4) (1817.2 mg ± (b) (4)
3.2	**Degradation products (HPLC)**	
	(b) (4)	≤ (b) (4) %
	Unidentified degradation product, each	≤ %
	Total sum of degradation products	≤ %
4	**ASSAY (HPLC)**	
4.1	**Content of macimorelin**	
	Average content of macimorelin related to the theoretical content (b) (4	(b) (4) % ((b) (4) mg)
4.2	**Uniformity of dosage units (Content uniformity) (USP<905> / Ph. Eur. 2.9.40) a)**	The acceptance value of the first 10 dosage units is (b) (4) (b) (4) . If the acceptance value is (b) (4) (b) (4) test the next 20 units and proceed according to pharmacopoeia requirements.
5	**CONCENTRATION AFTER RECONSTITUTION (HPLC)**	
	Average concentration of macimorelin in drinking solution	(b) (4) ng/ml
6	**Microbiological examination of non-sterile products: microbial enumeration tests (USP<61> / Ph. Eur. 2.6.12) a)**	
	Total aerobic microbial count (TAMC)	≤ (b) (4) CFU/g
	Total combined yeasts/moulds count (TYMC)	≤ CFU/g
7	**Absence of Escherichia coli (USP<62> / Ph. Eur. 2.6.13) a)**	absent in 1 g

a) current edition

Table 5: Shelf-life specification

Test no.	Description	Shelf Life Specification
1	**DESCRIPTION**	White to off-white granules in aluminum foil (b) (4)
2	**IDENTITY**	
2.1	**Macimorelin (HPLC)**	The peak of macimorelin in the solution to be tested and the peak of macimorelin in the reference solution for assay have to be comparable in retention time (tR ± 0.3 min).
2.2	**Macimorelin (UV)**	The UV spectrum of the peak corresponding to macimorelin in the test solution has to be comparable with regard to shape and position of absorption bands to that of the macimorelin peak in the reference solution.
3	**PROPERTIES AND PURITY**	
3.2	**Degradation products (HPLC)**	
	(b) (4)	≤ (b) (4)
	Unidentified degradation product, each	≤
	Total sum of degradation products	≤
4	**ASSAY (HPLC)**	
4.1	**Content of macimorelin**	
	Average content of macimorelin related to the theoretical content (b) (4)	(b) (4) % ((b) (4) mg)
5	**CONCENTRATION AFTER RECONSTITUTION (HPLC)**	
	Average concentration of macimorelin in drinking solution	(b) (4) mg/ml
6	**Microbiological examination of non-sterile products: microbial enumeration tests (USP<61> / Ph. Eur. 2.6.12)** [a)]	
	Total aerobic microbial count (TAMC)	≤ (b) (4) CFU/g
	Total combined yeasts/moulds count (TYMC)	≤ CFU/g
7	**Absence of Escherichia coli (USP<62> / Ph. Eur. 2.6.13)** [a)]	absent in 1 g

a) current edition

Appendix 3. Drug Substance Specification

Table 8: Release specification of macimorelin acetate

Test no.	Test	Specification
1	DESCRIPTION	Off-white to pale yellow powder
2	IDENTITY	
2.1	Macimorelin (HPLC)	The peak of macimorelin in the solution to be tested and the peak of macimorelin in the reference solution for assay have to be comparable in retention time (± 0.3 min).
2.2	Macimorelin acetate (^{1}H-NMR)	Conforms to reference
2.3	Macimorelin (Specific optical rotation)	+19.0° ± 2.0°
2.4	Acetate (HPLC)	The peak of acetate in the solution to be tested and the peak of acetate in the reference solution for content of acetate have to be comparable with regard to retention time (tR ± 0.3 min).
3	PROPERTIES AND PURITY	
3.1	Residual solvents (GC)	
	(b) (4)	(b) (4)
3.2	Water content (Karl Fischer) (Ph. Eur. 2.5.12 / USP <921>)	
3.3	Sulphated ash (Ph. Eur. 2.4.14 / USP <281>)	
3.4	Heavy metals (USP <233>)	
	(b) (4)	
3.5	Related substances (HPLC)	
	(b) (4	
	Unidentified impurity, each	
	Total sum of impurities	
	(b) (4	
3.6		
4	ASSAY (HPLC)	

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Test no.	Test	Specification
4.1	**Content of macimorelin**	
	Content of macimorelin related to the water and acetate free substance	(b) (4) %
4.2	**Content of acetate**	(b) (4) %
5	**MICROBIAL ENUMERATION TEST (Ph. Eur. 2.6.12 / USP <61>)**	
	Total aerobic microbial count (TAMC)	Not more than (b) (4) CFU/0.1 g
	Total yeast and moulds count (TYMC)	Not more than CFU/0.1 g

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/s/

SUONG T TRAN
12/19/2013

DANAE D CHRISTODOULOU
12/19/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5 November 2013

TO: NDA 205598

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Master Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Abolade Adeolu, R.Ph., MS, MBA
Regulatory Project Manager
OND/DMEP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Macrilen (macimorelin acetate granules for oral solution) [Submission Date: 5 November 2013]

The Microbial Limits specification for Macrilen (granules for oral solution) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4) CFU/g
Total Yeast and Mold Count (USP <61>)	NMT CFU/g
E. coli (USP <62>)	Absent in 1 g

M E M O R A N D U M

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>.

The drug product will also be tested for Microbial Limits at expiry as part of the post-approval stability protocol.

The draft labeling for the drug product instructs the health care provider to dissolve the drug product granules in water and administer the solution within 30 minutes of preparation.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product granules is controlled via a suitable testing protocol and the post-constitution in-use period is appropriate for the maintenance of microbial quality.

END

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/s/

BRYAN S RILEY
11/05/2013

STEPHEN E LANGILLE
11/06/2013