CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214231Orig1s000

PRODUCT QUALITY REVIEW(S)

Memo for Corrections to OPQ Integrated Quality Assessment Submitted in DARRTS on 2/5/2021

Background: The OPQ integrated quality assessment for NDA 214231 was submitted in DARRTS on 02/5/2021. The overall OPQ recommendation for NDA 214231 is approval.

This memo is provided for documenting corrections related to expiration date & storage condition information provided in pages 7 and 8 of the OPQ Integrated Quality Assessment dated 2/5/2021 in DARRTS

Correction 1: Page 7 last paragraph – Revise the storage temperature information provided in the expiration date & storage condition section from:

"The application contains up to 36 months of long-term stability data (b) (4) *12 months of long-term stability data (25°C/60% RH), and 3 month accelerated stability (40°C/65% RH), for 6 stability batches manufactured at* (b) (4) *L scale."*

to the following:

"The application contains up to 36 months of long-term stability data (5°C), 12 months of long-term stability data (25°C/60% RH), and 3 month accelerated stability (40°C/65% RH), for 6 stability batches manufactured at (b) (4) (b) (4) *L scale".*

Correction 2: Revise the expiration period information provided at the top of Page 8 from:

"Based on available stability data, an expiration period of (b) (4) *months is granted when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 12 months in the protective case".*

to the following: *"Based on available stability data, an expiration period of 36 months is granted when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 12 months in the protective case".*

The revised expiration date & storage condition information in Pages 7 through 8 of the Integrated Quality Assessment should read as follows:

Expiration Date & Storage Conditions: The application contains up to 36 months of long-term stability data (5°C), 12 months of long-term stability data (25°C/60% RH), and 3 month accelerated stability (40°C/65% RH) for 6 stability batches manufactured at (b) (4) *L scale. The product is sensitive light and should not be frozen. Based on available stability data, an expiration period of 36 months is granted when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 12 months in the protective case.*

The product needs to be discarded at the end of the 12-month period at room temperature storage, or after the expiration date stated on the product label , whichever occurs first. Please refer to the drug product review dated 11/20/20 in Panorama for additional information.

The data support the following labeling statements:

Store ZEGALOGUE in a refrigerator, 2°C to 8°C (36°F to 46°F). Keep away from the cooling element. Do not freeze.

ZEGALOGUE can be kept at room temperature (20°C to 25°C), for up to 12 months. Record the date when the product was removed from the refrigerator in the space provided on the protective case. Do not return the product to the refrigerator after storing at room temperature. Store in the provided protective case and protect from light.

Discard ZEGALOGUE after the end of the 12-month period at room temperature storage, or after the expiration date stated on the product, whichever occurs first.

OVERALL ASSESSMENT AND CONCLUSION: At present, there are no outstanding deficiencies related to the drug substance, drug product, process, facility, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA 214231 is approval.

Muthukumar Ramaswamy, Ph.D. 2/22/2021

Application Technical Lead Name and Date:

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
02/23/2021 03:58:55 PM

Recommendation: Approval

NDA 214231
Review 1

Drug Name/Dosage Form	Zegalogue (dasiglucagon) injection
Strength	0.6 mg/0.6 mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Zealand Pharma A/S
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-submission, Original submission, and amendments	Original submission: 3/27/20 Amendments: 4/24/2020 (DP stability), 5/12/2020 (Device), 6/01/20 (device), 6/8/2020 (micro), 8/13/2020 (micro), 8/17/2020 (manufacturing), 8/24/2020 (drug product), 9/18/2020 (device), 9/30/2020 (device), 10/02/2020, 10/23/2020 (facility follow up), 10/26/2020 (device), 11/02/20 (drug product), 11/12/20 (drug product), 11/17/20, 12/11/2020 and 2/01/2021 (label).	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Joseph Leginus/ Suong Tran	Branch III/Division of New Drug Active pharmaceutical
Drug Product	Muthukumar Ramaswamy / David J Claffey	Branch V/New Drug Products III
Process/ Facility	Laurie Nelson/Kumar Janoria	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Laura Wasil/ Yeissa Chabrier Rosello	OPMA
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/New Drug Products III
Environmental Analysis (EA)	Muthukumar Ramaswamy/ David J Claffey	Branch V/New Drug Products III of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	adequate	6/8/2020	LOA dated 10/2/2019
	III			Active	*	LOA dated 5/29/2019
	II			adequate	6/1/2020	LOA dated 11/14/2019
	V			adequate	5/18/2020	LOA dated 9/27/2019
	V			adequate	6/16/2020	LOA dated 5/19/2020
	III			Active	*	LOA dated 9/27/2019

*Sufficient information provided in the NA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127866	dasiglucagon injection

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm. Tox. (impurities)	Complete	Adequate (via email)	7/14/2020	Patricia Brundage

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 214231 is approval. This recommendation includes acceptable recommendation for all the facilities listed in the application. At present, there are no outstanding deficiencies associated with drug substance, drug product, environmental assessment, process, and microbiology sections of this application.

II. Summary of Quality Assessments

A. Product Overview

Dasiglucagon hydrochloride is a new molecular entity and an analogue of human glucagon. It is a 29-amino acid peptide. Dasiglucagon is an anti-hypoglycemic agent. The proposed drug, Zegalogue (dasiglucagon) injection, 0.6 mg/0.6mL is for emergency to rescue patients having severe hypoglycemia. Zegalogue is a clear, colorless sterile solution provided as a single-dose pre-filled syringe or as an auto-injector. Each syringe contains 0.6 mg dasiglucagon provided as dasiglucagon hydrochloride.

Zegalogue is formulated in an aqueous solution containing tris buffer and sodium chloride as a clear, colorless sterile solution with a target pH of 6.5. Zegalogue should be stored at 2°C to 8°C (36°F to 46°F) for up to 24 months protected away from light in a protective case in the carton. During shelf-life, the Zegalogue may be stored at 25°C ± 2°C for 12 months in the protective case.

Dasiglucagon injection is a drug-device combination product. CDER OPQ review covers the product quality aspects of the drug-device combination product. CDRH review covers the device aspects of the combination product.

Proposed Indication(s) including Intended Patient Population	Treating adults and children over 6 years having severe hypoglycemia
Duration of Treatment	emergency use
Maximum Daily Dose	0.6mg dose for each rescue
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Note: The initial OPQ integrated quality assessment for NDA 214231 was submitted in DARRTS on 11/27/2020 indicating that the overall manufacturing inspection recommendation (OMIR) for NDA 214231 was pending at that time. This review contains the updated overall

manufacturing inspection recommendation and the final OPQ recommendation for NDA 214231.

Drug Substance

The drug substance, dasiglucagon is a 29-amino acid peptide with free N-terminal and C-terminal carboxylic acid. The drug substance is provided as a hydrochloride salt. Dasiglucagon is a glucagon analog. The chemical name of dasiglucagon hydrochloride is as follows:

L-Histidyl-L-seryl-L-glutaminylglycyl-L-threonyl-Lphenylalanyl-L-threonyl-L-seryl-L-aspartyl-Ltyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-aspartyl-α-aminoisobutyryl-L-alanyl-L-arginyl-L-alanyl-Lglutamyl-L-glutamyl-L-phenylalanyl-L-valyl-L-lysyl-L-tryptophyl-L-leucyl-L-glutamyl-L-seryl-L-threonine, hydrochloride salt

The molecular formula and molecular weight of free base is respectively $C_{152}H_{222}N_{38}O_{50}$ and 3381.6 g/mol (average mass). Dasiglucagon is an amorphous powder and is freely soluble in water.

Dasiglucagon is synthesized by (b) (4) The applicant referenced (b) (4) Type II DMF (b) (4) for all CMC information related to the drug substance (Letter of authorization dated 11/14/2019). Only limited CMC information is provided in the NDA.

Dr. Joseph Leginus reviewed the chemistry, manufacturing, and control information for the drug substance in the NDA 214231 as well in the DMF (b) (4) His review covered the drug substance manufacturing process description, the proposed starting material specifications, control strategy for impurities, characterization data for drug substance and its impurities, reference standard information, test method descriptions and methods validation, drug substance specifications, and stability data provided in the DMF. His review concluded that the drug substance information in the DMF and in the NDA is adequate to control the quality of the drug substance used in the drug product manufacturing.

Based on review of the stability information, Dr. Leginus granted a retest period of (b) (4) months for the drug substance when stored (b) (4) (b) (4) Dr. Leginus' s recommendation for this application is adequate. For additional details, please refer to Dr. Leginus' s CMC reviews for drug substance available under NDA 214231 (dated 6/30/2020) and DMF (b) (4) (dated 6/1/2020) in Panorama.

Drug Product

Drug Product Formulation: The proposed product, Zegalogue (dasiglucagon) injection, 0.6 mg/0.6mL is a clear, colorless, sterile, aqueous solution packaged in a 1.0 mL single-dose pre-filled syringe or as auto-injector. Each mL contains 1.0 mg of dasiglucagon (provided as dasiglucagon hydrochloride) solubilized in (b) (4) tromethamine (tris

buffer), sodium chloride, and water for injection. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to 6.5. The composition of the proposed commercial product is the same as the one used during Phase 1 and Phase 3 studies.

The commercial presentation (pre-filled syringe) was used for Phase 2 and 3 studies. The primary container closure system consists of a siliconized 1 mL (b) (4) (b) (4) glass syringe fitted with a 27G x ½ inch staked needle and rigid needle shield (RNS) on one end and a (b) (4) plunger on the other end. The final product is provided in a protective case. Storage of the product in the protective case is recommended to prevent exposure to light during shelf-life. The container closure components proposed for use in the product are known for use in approved products and the applicant provided leachable study assessment to assure the safety of the proposed container closure system.

Dr. Ramaswamy reviewed the drug product information including drug product composition, drug product specification, excipient information, analytical methods, container closure system, compatibility information, and stability data. The compatibility of the active ingredient with excipients and the container closure components is supported by drug product stability data.

The drug product is tested for visual appearance (color and clarity), identity, sub-visible particulate matter, pH, osmolality, assay, purity and impurities including (b) (4) (b) (4) extractable volume, uniformity of dosage units, closure integrity, deliverable volume (syringe), dose accuracy (auto-injector), gliding and break loose force, endotoxin content, and sterility. The drug product conforms to USP <1> injection, USP <788> particulate matter, US<71> sterility, USP <785> osmolality, USP <697> container content for injections, and USP <85> bacterial endotoxin. Dr. Ramaswamy concluded that the proposed specification is adequate to support the quality of the proposed product. Please refer to the drug product review dated 11/20/2020 for additional information.

Manufacturing Process and Controls: The manufacturing process involves (b) (4) (b) (4)

The applicant is using batch record instructions and the following (b) (4) control tests to control quality of the product: (b) (4) (b) (4) (b) (4) Process/review also covers manufacturing process risk assessment for critical quality attributes and concluded that overall risk is low.

The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in phase 3 clinical and registration stability studies are the same as that proposed for commercial use. The batch size of registration stability batches ranged from (b) (4) L The proposed commercial batch size is (b) (4) L.

No overage and no reprocessing will be employed in the manufacture of this drug product. For detailed information on the manufacturing process and process controls, refer to process review dated 11/23/2020 in Panorama. The process reviewer concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Microbiological control information: Microbiology reviewer, Dr. Wasil reviewed the microbiological controls used in the drug product manufacturing process including (b) (4) drug product specifications for sterility, container closure integrity, endotoxin, (b) (4) validation, depyrogenation and component sterilization, media fill studies, hold times, and post-approval stability commitment. Dr. Wasil also reviewed the depyrogenation and sterilization and validation information provided in Type V DMF (b) (4) DMF (b) (4) and DMF (b) (4) (b) (4) Her review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. Wasil dated 6/12/2020 in Panorama.

Control Strategy: The critical quality attributes of the product are controlled through batch records instructions, process design including control of product exposure to light during manufacturing, excipient specifications including bioburden and endotoxin control, drug substance specification, component specifications for incoming container closure components, (b) (4) (b) (4) controls for the amounts of critical excipients added to the bulk solution, bioburden, visual verification of dissolution of excipients, product pH verification, (b) (4) integrity, and adequate finished product specification.

The proposed control strategy is adequate to assure the quality of the product. For additional information, please refer to the following CMC reviews in Panorama: Dr. Leginus's drug substance review dated 7/16/2020, Dr. Wasil 's microbiology review dated 6/12/2020, Dr. Ramaswamy's drug product review dated 11/20/2020 and Nelson's process reviews dated 11/23/2020.

Facility compliance information: Facility compliance information for the drug product and drug substance manufacturing and testing facilities was reviewed by OPMA reviewer, Laurie Nelson. Her review concluded that the facilities associated with the application are adequate to support the application. Thus, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is approve. Panorama screen shot of the submission

facility status is shown below. For additional details, please refer to Process/facility reviews in Panorama dated 11/23/2020 and 1/29/2021.

Time run: 2/5/2021 11:02:47 AM

Latest Submission Manufacturing Status for NDA-214231-Original-1

Latest Overall Manufacturing Inspection Recommendation	Inspection Requested	Inspection Completed	pOAI/OAI Alerts	Pending Profile
Approve Completion Date: 2/2/2021 NDA-214231-ORIG-1	0	1	No	No

Hint: Click Facility ID link to open Facility Program
Click Facility Name to open Facility Status View: Detail
Click here to Refresh the Report

Facility ID	FEI	Facility DUNS	Facility Name	Latest Facility Status /As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason
			(b) (4)	No Evaluation Necessary 5 /1 /2020	(b) (4)	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** OTHER TESTER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** RELEASE TESTER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
110175486	3009188105		RECHON LIFE SCIENCE AB	No Evaluation Necessary 5 /1 /2020	SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**Product Supply Chain:** STORER: DASIGLUCAGON	Compliant	
			(b) (4)	No Evaluation Necessary 5 /1 /2020	(b) (4)	**Product Supply Chain:** OTHER TESTER: DASIGLUCAGON	Compliant	
				Approve Facility 4 /27 /2020 Based on File Review		**Product Supply Chain:** STERILITY TESTER: DASIGLUCAGON	Compliant	
110003444	3002806978	775207769	RECHON LIFE SCIENCE AB	Approve Facility 1 /29 /2021 Based on File Review	IDD INJECTABLE DELIVERY DEVICE	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON LABELER: DASIGLUCAGON PACKAGER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STABILITY TESTER: DASIGLUCAGON STORER: DASIGLUCAGON **Substance Supply Chain:** STORER: DASIGLUCAGON	Compliant	
				Approve Facility 1 /29 /2021 Based on File Review	SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON LABELER: DASIGLUCAGON PACKAGER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STABILITY TESTER: DASIGLUCAGON STORER: DASIGLUCAGON **Substance Supply Chain:** STORER: DASIGLUCAGON	Compliant	
			(b) (4)	Approve Facility 5 /1 /2020 Based on File Review	(b) (4)	**Substance Supply Chain:** MANUFACTURER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STORER: DASIGLUCAGON	Compliant	
				Approve Facility 1 /29 /2021		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON	Compliant	

Environmental assessment: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(b) and 25.21 as the action on this NDA may not significantly affect the quality of the human environment. The estimated concentration of the drug substance at the point of entry into the aquatic environment would be below 0.1part per billion (0.1 ppb). Dr. Ramaswamy granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 11/20/20 for additional information.

Expiration Date & Storage Conditions: The application contains up to 36 months of long-term stability data (b) (4) 12 months of long-term stability data (25°C/60% RH), and 3 month accelerated stability (40°C/65% RH), for 6 stability batches manufactured at (b) (4) L scale. Dr. Ramaswamy reviewed the stability

information. The product is sensitive light and should not be frozen. *Based on available stability data, an expiration period of* (b) (4) *months is granted when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 12 months in the protective case*. Please refer to the drug product review dated 11/20/20 in Panorama for additional information.

Container and Carton Label Review: The drug product reviewer completed review of the container and carton label. Comments related to the carton and container label (e.g., package description, salt equivalency statement pertaining to strength, established name, and storage conditions) will be resolved during OND labeling review. Refer to the Dr. Ramaswamy's labeling review dated 11/20/2020 for additional information.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, facility, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA *214231 is approval.*

Muthukumar Ramaswamy, Ph.D. 2/5/2021

Application Technical Lead Name and Date:

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
02/05/2021 03:53:31 PM

QUALITY ASSESSMENT

Recommendation: Pending

NDA 214231
Review 1

Drug Name/Dosage Form	Zegalogue (dasiglucagon) injection
Strength	0.6 mg/0.6 mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Zealand Pharma A/S
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-submission, Original submission, and amendments	Original submission: 3/27/20 Amendments: 4/24/2020 (DP stability), 5/12/2020 (Device), 6/01/20 (device), 6/8/2020 (micro), 8/13/2020 (micro), 8/17/2020 (manufacturing), 8/24/2020 (drug product), 9/18/2020 (device), 9/30/2020 (device), 10/02/2020, 10/23/2020 (facility follow up), 10/26/2020 (device), 11/02/20 (drug product), 11/12/20 (drug product) and 11/17/20 (label).	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Joseph Leginus/ Suong Tran	Branch III/Division of New Drug Active pharmaceutical
Drug Product	Muthukumar Ramaswamy / David J Claffey	Branch V/New Drug Products III
Process/ Facility	Laurie Nelson/Kumar Janoria	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Laura Wasil/ Yeissa Chabrier Rosello	OPMA
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/New Drug Products III
Environmental Analysis (EA)	Muthukumar Ramaswamy/ David J Claffey	Branch V/New Drug Products III of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	adequate	6/8/2020	LOA dated 10/2/2019
	III			Active	*	LOA dated 5/29/2019
	II			adequate	6/1/2020	LOA dated 11/14/2019
	V			adequate	5/18/2020	LOA dated 9/27/2019
	V			adequate	6/16/2020	LOA dated 5/19/2020
	III			Active	*	LOA dated 9/27/2019

*Sufficient information provided in the NA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127866	dasiglucagon injection

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm. Tox. (impurities)	Complete	Adequate (via email)	7/14/2020	Patricia Brundage

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommendation for NDA 214231 is pending. At this time, the manufacturing facility assessment for Rechon Life Sciences AB, the finished product manufacturer is still in progress Therefore, the overall manufacturing inspection recommendation (OMIR) is pending. At present, there are no outstanding deficiencies associated with drug substance, drug product, environmental assessment process, and microbiology sections of this application.

II. Summary of Quality Assessments

A. Product Overview

Dasiglucagon hydrochloride is a new molecular entity and an analogue of human glucagon. It is a 29-amino acid peptide. Dasiglucagon is an anti-hypoglycemic agent. The proposed drug, Zegalogue (dasiglucagon) injection, 0.6 mg/0.6mL is for emergency to rescue patients having severe hypoglycemia. Zegalogue is a clear, colorless sterile solution provided as a single-dose pre-filled syringe or as an auto-injector. Each syringe contains 0.6 mg dasiglucagon provided as dasiglucagon hydrochloride.

Zegalogue is formulated in an aqueous solution containing tris buffer and sodium chloride as a clear, colorless sterile solution with a target pH of 6.5. Zegalogue should be stored at 2°C to 8°C (36°F to 46°F) for up to 24 months protected away from light in a protective case in the carton. During shelf-life, the Zegalogue may be stored (b) (4) (b) (4) for 12 months in the protective case.

Dasiglucagon injection is a drug-device combination product. CDER OPQ review covers the product quality aspects of the drug-device combination product. CDRH review covers the device aspects of the combination product.

Proposed Indication(s) including Intended Patient Population	Treating adults and children over 6 years having severe hypoglycemia
Duration of Treatment	emergency use
Maximum Daily Dose	0.6mg dose for each rescue
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance

The drug substance, dasiglucagon is a 29-amino acid peptide with free N-terminal and C-terminal carboxylic acid. The drug substance is provided as a hydrochloride salt.

Dasiglucagon is a glucagon analog. The chemical name of dasiglucagon hydrochloride is as follows:

L-Histidyl-L-seryl-L-glutaminylglycyl-L-threonyl-Lphenylalanyl-L-threonyl-L-seryl-L-aspartyl-Ltyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-aspartyl-α-aminoisobutyryl-L-alanyl-L-arginyl-L-alanyl-Lglutamyl-L-glutamyl-L-phenylalanyl-L-valyl-L-lysyl-L-tryptophyl-L-leucyl-L-glutamyl-L-seryl-L-threonine, hydrochloride salt

The molecular formula and molecular weight of free base is respectively $C_{152}H_{222}N_{38}O_{50}$ and 3381.6 g/mol (average mass). Dasiglucagon is an amorphous powder and is freely soluble in water.

Dasiglucagon is synthesized by (b) (4) The applicant referenced (b) (4) Type II DMF (b) (4) for all CMC information related to the drug substance (Letter of authorization dated 11/14/2019). Only limited CMC information is provided in the NDA.

Dr. Joseph Leginus reviewed the chemistry, manufacturing, and control information for the drug substance in the NDA 214231 as well in the DMF (b) (4). His review covered the drug substance manufacturing process description, the proposed starting material specifications, control strategy for impurities, characterization data for drug substance and its impurities, reference standard information, test method descriptions and methods validation, drug substance specifications, and stability data provided in the DMF. His review concluded that the drug substance information in the DMF and in the NDA is adequate to control the quality of the drug substance used in the drug product manufacturing.

Based on review of the stability information, Dr. Leginus granted a retest period of (b) (4) months for the drug substance when stored (b) (4) (b) (4) Dr. Leginus' s recommendation for this application is adequate. For additional details, please refer to Dr. Leginus' s CMC reviews for drug substance available under NDA 214231 (dated 6/30/2020) and DMF (b) (4) (dated 6/1/2020) in Panorama.

Drug Product

Drug Product Formulation: The proposed product, Zegalogue (dasiglucagon) injection, 0.6 mg/0.6mL is a clear, colorless, sterile, aqueous solution packaged in a 1.0 mL single-dose pre-filled syringe or as auto-injector. Each mL contains 1.0 mg of dasiglucagon (provided as dasiglucagon hydrochloride) solubilized in (b) (4)/tromethamine (tris buffer), sodium chloride, and water for injection. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to 6.5. The composition of the proposed commercial product is the same as the one used during Phase 1 and Phase 3 studies.

The commercial presentation (pre-filled syringe) was used for Phase 2 and 3 studies. The primary container closure system consists of a siliconized 1 mL (b) (4) (b) (4) glass syringe fitted with a 27G x ½ inch staked needle and rigid needle shield (RNS) on one end and a (b) (4) plunger on the other end. The final product is provided in a protective case. Storage of the product in the protective case is recommended to prevent exposure to light during shelf-life. The container closure components proposed for use in the product are known for use in approved products and the applicant provided leachable study assessment to assure the safety of the proposed container closure system.

Dr. Ramaswamy reviewed the drug product information including drug product composition, drug product specification, excipient information, analytical methods, container closure system, compatibility information, and stability data. The compatibility of the active ingredient with excipients and the container closure components is supported by drug product stability data.

The drug product is tested for visual appearance (color and clarity), identity, sub-visible particulate matter, pH, osmolality, assay, purity and impurities including (b) (4) (b) (4) extractable volume, uniformity of dosage units, closure integrity, deliverable volume (syringe), dose accuracy (auto-injector), gliding and break loose force, endotoxin content, and sterility. The drug product conforms to USP <1> injection, USP <788> particulate matter, US<71> sterility, USP <785> osmolality, USP <697> container content for injections, and USP <85> bacterial endotoxin. Dr. Ramaswamy concluded that the proposed specification is adequate to support the quality of the proposed product. Please refer to the drug product review dated 11/20/2020 for additional information.

Manufacturing Process and Controls: The manufacturing process involves (b) (4) (b) (4)

The applicant is using batch record instructions and the following (b) (4) to control quality of the product: weight of active ingredient, pH, fill weight, (b) (4) bioburden control for bulk solution, (b) (4) container closure integrity, and visual inspection of the product. Process/review also covers manufacturing process risk assessment for critical quality attributes and concluded that overall risk is low.

The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in phase 3 clinical and registration stability studies are the same as that proposed for commercial use. The batch

size of registration stability batches ranged from (b) (4) L The proposed commercial batch size is (b) (4) L.

No overage is used. No reprocessing will be employed in the manufacture of this drug product. For detailed information on the manufacturing process and process control, refer to s process review dated 11/23/2020 in Panorama. The process reviewer concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Microbiological control information: Microbiology reviewer, Dr. Wasil reviewed the microbiological controls used in the drug product manufacturing process including (b) (4) drug product specifications for sterility, container closure integrity, endotoxin, (b) (4) validation, depyrogenation and component sterilization, media fill studies, hold times, and post-approval stability commitment. Dr. Wasil also reviewed the depyrogenation and sterilization and validation information provided in Type V DMF (b) (4) DMF (b) (4) and DMF (b) (4) (b) (4) Her review concluded that the proposed microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. Wasil dated 6/12/2020 in Panorama.

Control Strategy: The critical quality attributes of the product are controlled through batch records instructions, process design including control of product exposure to light during manufacturing, excipient specifications including bioburden and endotoxin control, drug substance specification, component specifications for incoming container closure components, (b) (4) (b) (4) controls for the amounts of critical excipients added to the bulk solution, bioburden, visual verification of dissolution of excipients, product pH verification, (b) (4) integrity, and adequate finished product specification.

The proposed control strategy is adequate to assure the quality of the product. For additional information, please refer to the following CMC reviews in Panorama: Dr. Leginus's drug substance review dated 7/16/2020, Dr. Wasil 's microbiology review dated 6/12/2020, Dr. Ramaswamy's drug product review dated 11/20/2020 and Nelson's process reviews dated 11/23/2020.

Facility compliance information: Facility compliance information for the drug product and drug substance manufacturing and testing facilities was reviewed by OPMA reviewer, Laurie Nelson. With the exception of drug product manufacturing facility located in Sweden (Rechon Life Sciences AB, FEI # 3002806978), the facility review for the remaining manufacturing facilities (b) (4) (b) (4) (b) (4) are complete and acceptable. Rechon Life Sciences AB is the drug product manufacturer and responsible for the assembly of pre-filled syringe into auto-injector. Due to COVID 19 public health situation and current travel restrictions, a 704a document review has been initiated to

determine if a facility inspection is required at Rechon Life Sciences AB. At this time, 704a document review is in progress and a final facility recommendation is pending. CDRH reviewer has recommended a post-approval inspection for (b) (4) (b) (4) the developer and manufacturer of the auto-injector front and rear assembly.

Time run: 11/27/2020 10:05:58 AM

Latest Submission Manufacturing Status for NDA-214231-Original-1

Latest Overall Manufacturing Inspection Recommendation	Inspection Requested	Inspection Completed	pOAI/OAI Alerts	Pending Profile
Pending Completion Date: NDA-214231-ORIG-1	1	0	No	No

Hint: Click Facility ID link to open Facility Program
Click Facility Name to open Facility Status View: Detail
Click here to Refresh the Report

Facility ID	FEI	Facility DUNS	Facility Name	Latest Facility Status /As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason
110003444	3002806978	775207769	RECHON LIFE SCIENCE AB	Pending	IDD INJECTABLE DELIVERY DEVICE	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON LABELER: DASIGLUCAGON PACKAGER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STABILITY TESTER: DASIGLUCAGON STORER: DASIGLUCAGON **Substance Supply Chain:** STORER: DASIGLUCAGON	Compliant	
				Pending	SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON LABELER: DASIGLUCAGON PACKAGER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STABILITY TESTER: DASIGLUCAGON STORER: DASIGLUCAGON **Substance Supply Chain:** STORER: DASIGLUCAGON	Compliant	
(b) (4)				No Evaluation Necessary 5 /1 /2020	(b) (4)	**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** OTHER TESTER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** RELEASE TESTER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** STORER: DASIGLUCAGON	Compliant	
				No Evaluation Necessary 5 /1 /2020		**Product Supply Chain:** OTHER TESTER: DASIGLUCAGON	Compliant	
				Approve Facility 4 /27 /2020 Based on File Review		**Product Supply Chain:** STERILITY TESTER: DASIGLUCAGON	Compliant	
				Approve Facility 5 /1 /2020 Based on File Review		**Substance Supply Chain:** MANUFACTURER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON STORER: DASIGLUCAGON	Compliant	
				Approve Facility 9 /21 /2020 Based on File Review		**Product Supply Chain:** MANUFACTURER: DASIGLUCAGON RELEASE TESTER: DASIGLUCAGON	Compliant	

Thus, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is pending. The Panorama screen shot facility assessment recorded on 11/24/2020 is shown below. For additional details, please refer to Process/facility review in Panorama dated 11/23/2020.

Environmental assessment: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(b) and 25.21 as the action on this NDA may not significantly affect the quality of the human environment. The estimated concentration of the drug substance at the point of entry into the aquatic environment would be below 0.1part per

billion (0.1 ppb). Dr. Ramaswamy granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 11/20/20 for additional information.

Expiration Date & Storage Conditions: The application contains up to 36 months of long-term stability data (b) (4) 12 months of long-term stability data (25°C/60% RH), and 3 month accelerated stability (40°C/65% RH), for 6 stability batches manufactured at (b) (4) L scale. Dr. Ramaswamy reviewed the stability information. The product is sensitive light and should not be frozen. *Based on available stability data, an expiration period of (b) (4) months is granted when stored at 2°C to 8°C (36°F to 46°F), during which the drug product can be stored at 25°C (77°F) for 12 months in the protective case*. Please refer to the drug product review dated 11/20/20 in Panorama for additional information.

Container and Carton Label Review: The drug product reviewer completed review of the container and carton label. Comments related to the carton and container label (e.g., package description, salt equivalency statement pertaining to strength, established name, and storage conditions) will be resolved during OND labeling review. Refer to the Dr. Ramaswamy's labeling review dated 11/20/2020 for additional information.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, and environmental analysis sections of this NDA. Since the facility assessment for NDA 214231 is still in progress, the OPQ overall recommendation for NDA *214231 is pending* at this time.

Muthukumar Ramaswamy, Ph.D. 11/27/2020

Application Technical Lead Name and Date:

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

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: *Summary of issues*.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Revise to TRADENAME (dasiglucagon) injection for subcutaneous use
Established name(s)		Adequate.
Route(s) of administration		Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) • 0.6 mg/ 0.6 mL (b) (4) (b) (4) autoinjector • 0.6 mg/ 0.6 mL (b) (4) pre-filled (b) (4) syringe	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	**2.2 Administration Instructions**	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	PROPRIETARY NAME injection is a clear, colorless solution available as: • 0.6 mg/ 0.6 mL (b) (4) (b) (4) autoinjector • 0.6 mg/ 0.6 mL (b) (4) (b) (4) pre-filled (b) (4) syringe	Revise to state: **single-dose** auto injector (b) (4) pre-filled pen
Strength(s) in metric system		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		Adequate.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	PROPRIETARY NAME contains dasiglucagon, which is a glucagon analog and an anti-hypoglycemic agent (b) (4) (b) (4) Dasiglucagon is comprised of 29 amino acids (b) (4) (b) (4) (b) (4) The molecular formula of dasiglucagon (anhydrous, free-base) is $C_{152}H_{222}N_{38}O_{50}$ and its molecular mass is 3382 g/mol (anhydrous, free-base). Dasiglucagon hydrochloride has the following chemical structure: 	Include salt form description for drug substance (i.e., dasiglucagon hydrochloride).
Dosage form(s) and route(s) of administration		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		Include salt equivalency statement and specify quantities of each excipient and pH. Include the structure of dasiglucagon hydrochloride with X=3 to 5 HCl
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	PROPRIETARY NAME injection is a preservative free, sterile, aqueous, clear, and colorless solution for subcutaneous use in a prefilled syringe (b) (4) an auto-injector. Each prefilled syringe (b) (4) autoinjector contains 0.63 mg of dasiglucagon provided as dasiglucagon hydrochloride, which is a salt with 3-5 equivalents of hydrochloride and the following inactive ingredients: 3.82 mg tromethamine, 6.44 mg sodium chloride and water for injection as the excipients. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 6.5.	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		In adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		N/A
Statement of being sterile (if applicable)		Adequate.
Pharmacological/ therapeutic class		Adequate
Chemical name, structural formula, molecular weight	The molecular formula of dasiglucagon (anhydrous, free-base) is $C_{152}H_{222}N_{38}O_{50}$ and its molecular mass is 3382 g/mol (anhydrous, free-base).	Adequate with comment. Indicate that molecular formula and molecular weight is for anhydrous, free-base

If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa or pH)		N/A
For oral prescription drug products, include gluten statement if applicable	None.	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	Adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>PROPRIETARY NAME injection is a clear, colorless solution supplied as follows:
<table>
<tr><th>Presentation</th><th>Strength</th><th>Package Size</th><th>NDC number</th></tr>
<tr><td>(b) (4)
autoinjector</td><td>0.6 mg/ 0.6mL</td><td>1</td><td></td></tr>
<tr><td>(b) (4)
autoinjector</td><td>0.6 mg/ 0.6mL</td><td>2</td><td></td></tr>
<tr><td>(b) (4)
syringe</td><td>0.6 mg/ 0.6mL</td><td>1</td><td></td></tr>
<tr><td>(b) (4)
syringe</td><td>0.6 mg/ 0.6mL</td><td>2</td><td></td></tr>
</table></td><td>Single-dose auto injector and pre-filled pen</td></tr>
<tr><td>Strength(s) in metric system</td><td></td><td>Adequate.</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td></td><td>Revise as indicated.</td></tr>
</table>

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	**Recommended Storage and Handling** Store PROPRIETARY NAME (b) (4) in a refrigerator, 2°C to 8°C (36°F to 46°F). Keep away from the cooling element. Do not freeze. (b) (4) PROPRIETARY NAME can be kept at room temperature (b) (4) (b) (4) for (b) (4) up to 12 months. Record the date when the product was removed from the refrigerator in the space provided on the protective case. Do not return the product to the refrigerator after storing at room temperature. Store in the provided protective case and protect from light.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	See above.	Adequate.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)		Adequate. The shelf life and in-use conditions are supported by stability results.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	No information included.	N/A
Include information about child-resistant packaging	No Information included.	Not applicable

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of	Manufacturer's name provided	Adequate.

the manufacturer, distributor, and/or packer		

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
To be assessed

3.0 CARTON AND CONTAINER LABELING

Assessment of Container and Carton labeling: Adequate with comments

Preliminary comments for the label

a) Specify the correct established name*," (dasiglucagon) injection* " on the container, carton and protective case label.

b) If space permits State that the product is "single-dose auto-injector or single-dose prefilled pen" on the container label. State that the product is single-dose auto-injector or single-dose prefilled syringe on the carton label.

c) Include the salt equivalency statement to carton label. Describe the strength as follows: 0.6mg/0.6 mL*.

*Each 0.6 mL contains 0.6 mg of dasiglucagon, present as dasiglucagon hydrochloride. Hydrochloride composition varies. See prescribing information.

d) Describe the storage temperature in the following format for protective case, carton and container labels: °C (°F)

3.1 Container Label

Auto-injector

Prefilled syringe Label

Protective case label

3.2 Carton Labeling

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 11/20/2020 02:47:15PM
GUID: 508da7210002a0c0870017f6c83398f4

David Claffey

Digitally signed by David Claffey
Date: 11/20/2020 02:48:56PM
GUID: 508da71e00029e20b201195abff380c2

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214231
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Zegalogue® dasiglucagon/ 1.0 mg/mL
Route of Administration	Subcutaneous injection
Applicant Name	Zealand Pharma A/S
Therapeutic Classification/ OND Division	Division of Diabetes, Lipid Disorders, and Obesity
Manufacturing Site	Rechon Life Science AB
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
ECTD Sequence 0001 (1)	**3/27/2020**
ECTD Sequence 0009 (9)	**6/8/2020**
ECTD Sequence 0019 (19)	**8/13/2020**

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This submission provides for the initial marketing of the sterile drug-device combination product. Information requests sent on 12 May 2020 and 30 July 2020 and the information request responses received on 8 June 2020 and 13 August 2020 are covered in this review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
DMF (b) (4)

(b) (4)

DMF (b) (4)

(b) (4)

DMF (b) (4)

(b) (4)

S DRUG SUBSTANCE

The drug substance is not provided sterile; therefore, the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Module 3.2.P.1, Description and Composition of the Drug Product.pdf)
(Module 3.2.P.7, Container Closure System – Pre-filled Safety Syringe (Dasiglucagon, Injection).pdf)

- **Description of the drug product –** clear, colorless sterile solution, filled in a (b) (4) syringe with a staked needle, to a target volume of (b) (4) mL. The pre-filled syringes are further assembled with the label with (b) (4) plunger rod into a (b) (4) pre-filled safety syringe or into a (b) (4) auto-injector (see container closure system summary table below).

- **Drug product composition –**

Ingredient	Function	Quantity per mL	Quantity per syringe
Dasiglucagon drug substance	Active ingredient	1.0 mg	0.63 mg
(b) (4) Tromethamine (Tris)	(b) (4)		
Sodium chloride			
(b) (4) Hydrochloric acid	pH adjustment	q.s.	q.s.
(b) (4) Sodium hydroxide	pH adjustment	q.s.	q.s.
WFI	Solvent	Ad 1.0 mL	Ad 0.63 mL

- **Description of container closure system for the drug product –** The container closure system for the drug product includes a primary packaging system (pre-filled syringe) and two potential secondary packaging systems (pre-filled safety syringe or auto-injector) intended to protect the primary packaging system; see figures and summary tables below.

Primary Packaging System

(b) (4)

Component	Description	Suppler
Syringe with staked needle	(b) (4)	
Plunger		

Secondary Packaging System (No product contact)

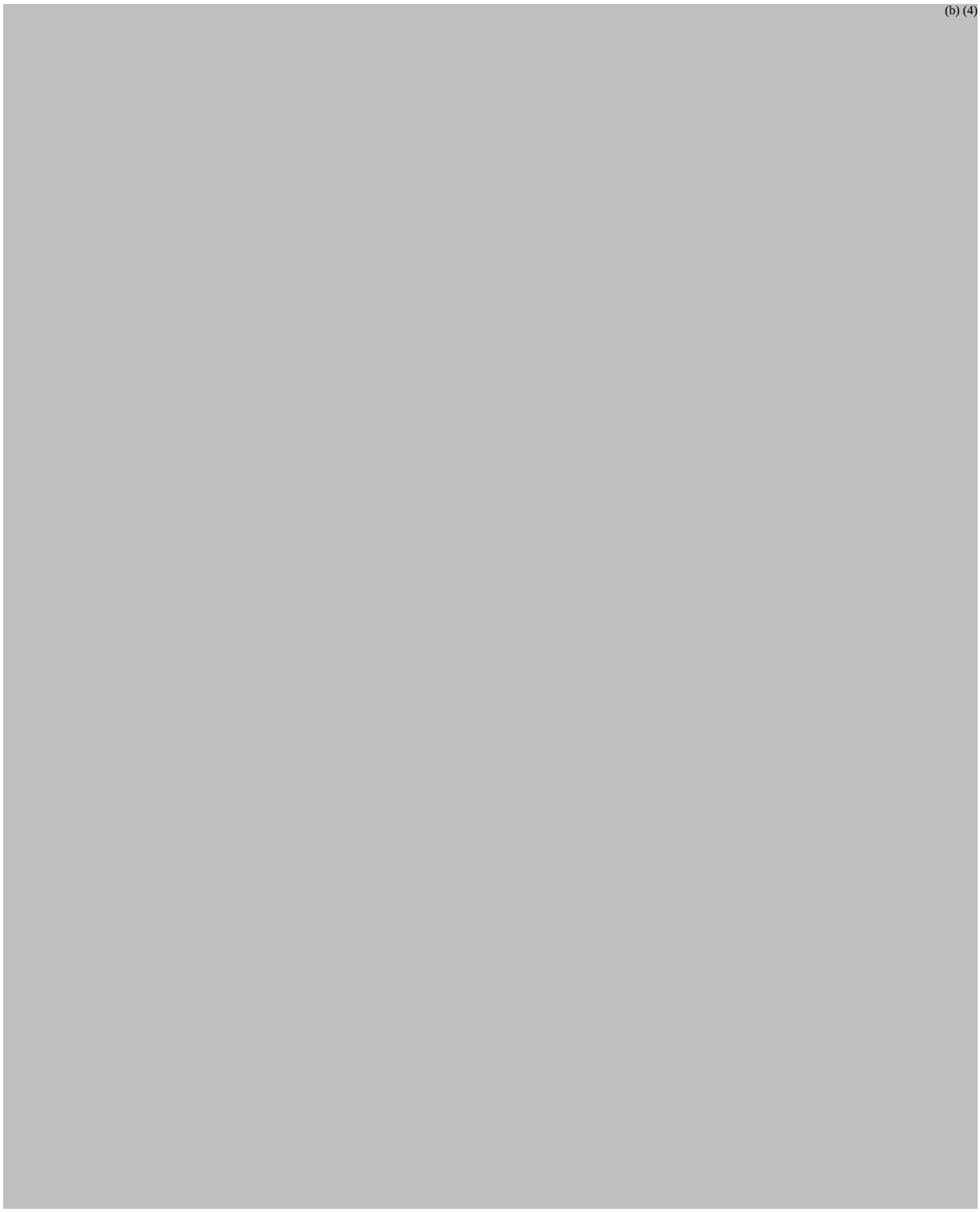
Presentation	Component	Description	Suppler
Pre-filled Safety Syringe	Rigid shield	Shield covering for the elastomeric needle shield	(b) (4)
	Plunger rod	(b) (4) rod used to depress plunger	
	(b) (4)		
	Protective Case	Rigid plastic case with lid; protects primary packaging from light, dust, mechanical stress	
Auto-injector	Rigid shield	Shield covering for the elastomeric needle shield	
	Auto-injector assembly components	See Module 3.2.P.7 for full description of auto-injector components	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)



26 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

P.5 CONTROL OF DRUG PRODUCT

P.5.1 SPECIFICATION

(Module 3.2.P.5.1, Specification – Pre-filled Syringe (Dasiglucagon, Injection)

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	Per USP <85>	< (b) (4) EU/mL*
Sterility	Per USP <71>	Complies

*Bacterial endotoxins specification was reduced from (b) (4) EU/mL to (b) (4) EU/mL in response to IRs sent on 12 May 2020.

Assessment: *Adequate*

The applicant has met regulatory expectations for the product release specifications.

P.5.2 ANALYTICAL PROCEDURES

Assessment: See Section P.5.1.

P.5.3 VALIDATION OF ANALYTICAL PROCEDURES

Endotoxins
(Module 3.2.P.5.3, Validation of Analytical Procedures (Dasiglucagon, Injection).pdf, page 55/56)

The applicant provided a summary of the method suitability testing for the bacterial endotoxins test method.

(b) (4)

Calculation of the Maximum Endotoxins Dose:

- The maximum dose per the package insert is 0.6 mg for both adults and children aged 6 years and older; administered as a single-dose subcutaneous injection.

- Calculated endotoxins dose at the proposed endotoxins specification and maximum dose:
    - Reviewer calculated endotoxins exposure for adult patients – (0.6 mg/hr ÷ 70 kg) x (b) (4) EU/mg = (b) (4) EU/kg/hr
    - Reviewer calculated endotoxins exposure for worst case pediatric patient (6 year old female) – (0.6 mg/hr ÷ 16 kg) x (b) (4) EU/mg = (b) (4) EU/kg/hr
- The maximum endotoxins dose at the proposed maximum endotoxins specification and maximum dose as calculated by this reviewer is not within the USP <85> recommendation of NMT 5 EU/kg/hr for pediatric patients.

In the Information Request dated 12 May 2020, the following deficiencies were issued:

9. *We acknowledge the summary information provided for suitability testing of the endotoxins test method (Module 3.2.P.5.3). However, please provide the method suitability study and results for further review. This should include a description of the test method (i.e., (b) (4) (b) (4), etc.), non-inhibitory dilution study and results, sample pH, inhibition and enhancement study and results, confirmation of (b) (4) sensitivity and product batch numbers used for the study.*

Applicant Response dated 8 June 2020: The applicant provided the following information:

10. *We note the endotoxins specification of < (b) (4) EU/mL. However, based on this specification, administration of the maximum dose (0.6 mg) to the worst-case patient based on weight (6 year old female, 3rd percentile) results in a maximum endotoxins exposure of (b) (4) EU/kg/hr, which exceeds the USP <85> recommendation of not more than 5 EU/kg/hr. Therefore, please revise the endotoxins specification such that the worst-case patient does not receive a maximum endotoxins exposure above 5 EU/kg/hr.*

Applicant Response dated 8 June 2020: The applicant reduced the endotoxin limit to < (b) (4) EU/mL.

Calculation of the maximum endotoxins dose for worst-case pediatric patients with the revised endotoxin specification:

- Reviewer calculated endotoxins exposure for worst case pediatric patient (6 year old female) – (0.6 mg/hr ÷ 16 kg) x (b) (4) EU/mg = (b) (4) EU/kg/hr
- The maximum endotoxins dose at the proposed maximum endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of NMT 5 EU/kg/hr for both adult and pediatric patients.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the test method, acceptance criteria and verification of the suitability of use of the endotoxins test that will be performed on the drug product prior to its release.

Sterility
(Module 3.2.P.5.3, Validation of Analytical Procedures (Dasiglucagon, Injection).pdf, page 54/56)

The applicant provided a summary for method suitability testing for sterility; the protocol and results were not provided.

(b) (4)

Assessment: *Adequate*

The applicant did not provide the protocol or results for method suitability testing of the sterility test method. However, since the method is performed per USP <71> and the summary provided all necessary information for the reviewer, additional information will not be requested at this time.

P.7 CONTAINER CLOSURE

Assessment: See Section P.1.

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION
(Module 3.2.P.8.1, Stability Summary and Conclusion (Dasiglucagon, Injection).pdf)

Stability testing was performed at the following storage conditions:

- Long-term storage conditions:
  - 5 ± 3°C/ambient RH
  - 5 ± 3°C/ambient RH (18 months, 24 months, 30 months) followed by 25 ± 2°C/60% RH (up to 36 months total)
  - 25 ± 2°C/60% RH (12 months)
- Accelerated storage conditions:

- 40 ± 2°C/75% RH (3 months).

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	Per USP <85>	< (b) (4) EU/mL*
Sterility	Per USP <71>	Complies

* Bacterial endotoxins specification was reduced from (b) (4) EU/mL to (b) (4) EU/mL in response to IRs sent on 12 May 2020.
CCIT is performed for informational purposes only and is not listed in the stability specification.

Proposed testing schedule for the exhibit batches is as follows:

Stability storage conditions: 5 ± 3°C/ambient RH

Test	Time (Months)							
	0	3	9	12	18	24	30	36
Bacterial Endotoxin	X			X		X	X	X
Sterility	X			X		X	X	X

Stability storage conditions: 25 ± 2°C/60% RH

Test	Time (Months)							
	0	3	9	12	18	24	30	36
Bacterial Endotoxin	X					X	X	X
Sterility	X					X	X	X

Proposed expiry: 36 months for storage at 2-8°C; 12 months for storage at room temperature (up to 25°C). The proposed expiry is applicable to both the pre-filled safety syringe and auto-injector configurations.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the proposed expiration date.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(Module 3.2.P.8.2, Stability Commitment for On-going Stability (Dasiglucagon, Injection).pdf)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	Per USP <85>	< (b) (4) EU/mL*
Sterility	Per USP <71>	Complies

* Bacterial endotoxins specification was reduced from (b) (4) EU/mL to (b) (4) EU/mL in response to IRs sent on 12 May 2020.

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 5 ± 3°C/ambient RH

Test	Time (Months)							
	0	3	9	12	18	24	30	36
Bacterial Endotoxin	X			X		X	X	X
Sterility	X			X		X	X	X

Stability storage conditions: 25 ± 2°C/60% RH

Test	Time (Months)							
	0	3	6	9	12	18	30	36
Bacterial Endotoxin	X		X		X		X	X
Sterility	X		X		X		X	X

Post Approval Stability Commitment

The applicant stated that three PPQ batches manufactured at the commercial manufacturing site (Rechon Life Science AB) were be placed in the stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 STABILITY DATA

(Module 3.2.P.8.3, Primary Stability Data for Dasiglucagon Injection in Pre-filled Syringe (Dasiglucagon, Injection).pdf)
(Module 3.2.P.8.3, Supportive Stability Data for Dasiglucagon Injection in Pre-filled Syringe (Dasiglucagon, Injection).pdf)

Accelerated and long-term stability studies were performed for drug product lots SK0049, TC0037, TG0103 and TG0104. An additional sub-batch of pre-filled syringes (TD0059) taken from batch SK0049 were stored for 6 months at 5°C followed by 12 months at 25°C; after release as batch TD0059, the sub-batch was stored for an additional 18 months at 5°C. The provided results, up to 36 months of stability data for some batches, showed that endotoxin and sterility specifications were met.

Assessment: *Adequate*

The stability data submitted to date support the microbiological quality of the subject drug product.

APPENDICES – N/A

R REGIONAL INFORMATION

Executed Batch Records
(Module 3.2.R)

Executed batch records were provided for drug product lots TG0104 and VL0159. The batch records confirm that sterilization/depyrogenation and (b) (4) manufacturing processes were used for the manufacture of the exhibit batches.

Assessment: *Adequate*

The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols

Assessment: Not applicable.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Prescribing Information

The product is not diluted prior to administration.

Storage conditions: 2-8°C. During shelf-life, the product can be kept at room temperature (up to 25°C) for a single period of up to 12 months; the label instructs the user to record the date when the product was removed from the refrigerator.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments

Assessment: See Section P.8.2.

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable.

Primary Microbiology Assessor Name and Date:
Laura R. Wasil, Ph.D.; 25 August 2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Yeissa Chabrier-Rosello, Ph.D.; 25 August 2020

Laura Wasil

Digitally signed by Laura Wasil
Date: 8/25/2020 12:34:43PM
GUID: 59b190cf009be8467b9b6b02d9543afe

Yeissa Chabrier Rosello

Digitally signed by Yeissa Chabrier Rosello
Date: 8/25/2020 12:40:08PM
GUID: 5317ea990000ce969cecabfa83284493

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
11/27/2020 12:27:06 PM