# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210134Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation: Approval**

# NDA 210134
# Review 1

| | |
|---|---|
| Drug Name/Dosage Form | Baqsimi (glucagon) nasal powder |
| Strength | 3mg |
| Route of Administration | Nasal |
| Rx/OTC Dispensed | Rx |
| Applicant | Eli Lilly and Company |
| US agent, if applicable | |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original and amendments | Original submission (6/28/2018) and amendments (9/20/2018, 10/23/2018, 11/01/2018, 11/30/2018, 1/2/2018, 1/28/2019, 2/28/2019, 3/01/2019, 3/04/2019 (CDRH), and 3/08/2019). | Quality module 3, 1.14 and 1.11 |

**Quality Review Team**

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Martin Haber | Branch II/New Drug API |
| Drug Product | Muthukumar Ramaswamy | Branch VI/New Drug Products II |
| Process/Microbiology | Ramesh Dandu | Branch IV/Process Assessment II |
| Facility | JoAnne Wang/Ramesh Dandu | Branch III/ Inspectional Assessment |
| Regulatory Business Process Manager | Anika Lalmansingh | Branch I/Regulatory Business Process Management I |
| Application Technical Lead | Muthukumar Ramaswamy | Branch VI/New Drug Products II |
| Environmental Analysis (EA) | Muthukumar Ramaswamy | Branch VI/New Drug Products II |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | Type II | | (b) (4) | Adequate | 3/13/2019 (Drug substance reviewer) | LOA 4/23/2018 |
| | Type III | | | Adequate (DMF review in Panorama dated 3/12/2019) | | LOA 2/29/2019, 1/3/2019, 4/4/2018 |
| | Type III | | | Adequate | 3/12/2019 | LOA 3/15/ 2018 |
| | Type IV | | | Adequate | 3/12/2019 | LOA 3/24/2017 |

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

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| Not applicable | | |

## 2. CONSULTS

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|---|
| Pharmacology/Toxicology | Complete | Acceptable. (Impurities and Leachables) | 3/5/19 | Dr. Dongyu Guo/ Dr. Lee Elmore |
| CDRH Compliance | Complete | Acceptable | 3/8/2019 | N. Thakur |

# Executive Summary

## I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality for NDA 210134 is approval. This recommendation includes acceptable recommendation from office of process and facilities for the facilities listed in the application.

## II. Summary of Quality Assessments

### A. Product Overview

This NDA is a 505(b)(1) application for Baqsimi (glucagon) nasal powder. Baqsimi is a single use, single dose, drug device combination product capable of delivering 3 mg glucagon intra nasally and is intended for rescuing adult and pediatric diabetic patients, who are in severe hypoglycemia. Administered dose should not be inhaled.

Baqsimi (glucagon) nasal powder is manufactured with device components supplied by (b) (4) and (b) (4) to manufacture the final product. In addition to glucagon, the powder contains beta-cyclodextrin and dodecylphosphocholine. Baqsimi is recommended for storage at temperature up to 30°C (86°F).

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | *Severe hypoglycemia* |
| **Duration of Treatment** | *Refer to CTDL memo* |
| **Maximum Daily Dose** | *3µg* |
| **Alternative Methods of Administration** | *Not applicable* |

### B. Quality Assessment Overview

**Drug Substance**

Glucagon is a 29 amino acid single chain polypeptide. Glucagon is manufactured by chemical synthesis. The amino acid sequence of synthetic glucagon is identical to endogenous glucagon. Glucagon used for manufacturing drug product is sourced from (b) (4). The applicant referenced Type II DMF (b) (4) ( (b) (4)) for CMC information pertaining to drug substance. DMF (b) (4) was reviewed by Dr. Martin T. Haber. His reviews for DMF (b) (4) and drug substance concluded that CMC information provided in DMF (b) (4) and drug substance (DS) section is adequate to support the NDA.

During development, the applicant also used a second source of drug substance ( (b) (4) for manufacturing the drug product batches (F14016-001 and F140423-001) used in clinical studies (IGBG, IGBH, B002, and B001). (b) (4) DS batches were used in remaining clinical studies including pivotal clinical studies and

PK/PD bridging clinical study. The applicant provided analytical comparability data to demonstrate the comparable quality of two sources of drug substance. Dr. Haber reviewed this information and concurred with the applicant's conclusion. For additional details, please refer to CMC review for drug substance in Panorama dated 3/13/2019.

**Drug Product**

*Drug Product Formulation:* The proposed nasal glucagon powder is a white (b) (6) powder filled in a single use nasal delivery device. To dispense the dose, the tip of the device is inserted into one nostril and the device is actuated. The device delivers 3mg of glucagon in nasal cavity. The product is not intended for inhalation. Drug deposited in the nasal cavity is absorbed without additional effort.

The single use nasal delivery device is packaged in a tube containing a molded desiccant and shrink wrapped for protection from moisture. Each single use device contains 3mg of glucagon, (b) (4) mg of beta cyclodextrin (BCD), and (b) (4) mg of dodecylphosphocholine (DPC).

(b) (4). The role of the two added excipients in the proposed product (DPC and BCD) (b) (4) Use of beta-cyclodextrin in pharmaceutical products is known. DPC is considered a novel excipient. Its use in the product is supported non-clinical and clinical studies.

The composition of the drug product remained the same during product development. Excipient suppliers and device component remained the same during development and commercial scale batches manufacturing. Drug product batches used in earlier clinical studies (small scale) were scaled up to commercial scale with modifications and validated at (b) (4) kg scale. The batches used in PK/PD bridging study and registration stability studies were manufactured at commercial scale.

Nasal glucagon powder is obtained by (b) (4)

(b) (4)

The [redacted] powder is hygroscopic. Product exposure to moisture during storage and handling is controlled [redacted]

The applicant's control strategy for producing acceptable quality product is [redacted]

Dr. Ramesh Dandu and Dr. Joanne Wang reviewed the manufacturing process and control information including microbiological control of the process. In addition, they reviewed the facility information for drug substance and combination product manufacturing and packaging facilities with additional input from ORA and CDRH compliance reviewer. Dr. Wang performed the pre-approval inspection with ORA at the combination product manufacturing facility ([redacted]). Their review concluded that information provided in process and facilities is acceptable to support the approval of this NDA. Please refer to process/facilities review in Panorama dated 3/12/2019.

During development, the applicant made changes to the manufacturing process and device. Device operating principles remained the same but minor changes were implemented to molded components and secondary packaging. The applicant performed analytical comparability assessment to support the comparability of batches used in various clinical studies and registration stability. Comparability assessment included physicochemical characterization of powders, product quality attributes (purity, potency, and biological activity), and device performance attributes (spray pattern, plume geometry, shot weight, and actuation force). With the exception of differences in PSD and particle morphology and accelerated stability profile, the CMC analytical comparability assessment indicated that the drug powder and combination product from commercial and clinical trial processes were comparable with respect to potency, bioactivity, degradation mechanisms and device performance attributes.

The finished product specification was finalized by the drug product reviewer. CDRH is finalizing the specification for the device actuation force. The drug product is tested for description (visual appearance), identity, assay, uniformity of dosage units, foreign particulate matter, impurities, delivered dose uniformity, [redacted] shot weight, [redacted], and particle size distribution. The quality attributes considered for inclusion in the drug product specification are in alignment with the attributes recommended for nasal powder under USP <5> Inhalation and nasal drug products – general information nasal product quality tests and powder, USP <601>

Inhalation and nasal drug products: aerosols, sprays and powders – performance quality tests and <905> Uniformity of dosage units.

Test for microbial limit is not included as part of the specification. This was considered acceptable based on the following considerations: (b) (4) of the product, process and manufacturing controls, container closure design (use of desiccant in secondary packaging) and real-time stability data supporting the acceptability of the product (Refer to process review for additional details).

The applicant performed a risk assessment per ICH Q3D and provided justification for not including routine elemental impurities testing in the product. This was considered acceptable by the drug product reviewer.

Potency of the finished will be determined by chemical assay. A bioassay is not part of the finished product specification. The applicant provided adequate bioassay data from stability studies to demonstrate the correlation between chemical assay and bioassay. Further the chemical assay is less variable. Use of bioassay as a characterization test is acceptable from the drug product reviewer perspective.

The combination product is labeled to dispense a mean of 3 mg glucagon per actuation. At the end of shelf-life, the mean dose dispensed from the device can be as low as (b) (4) mg glucagon with an understanding 90% of the samples tested will have a potency of (b) (4) mg and the potency of the remaining of the sample population may lie between (b) (4) mg. The (b) (4) mg lower limit for the dispensed dose at the end of shelf-life was based on discussio with clinical and clinical pharmacology reviewers and PK/PD model predicted profile comparison provided by the applicant for NG 3 mg and NG 2 mg with commercially representative drug product and IMG 1 mg. The (b) (4) is an acceptable lower limit for delivered dose (clinically effective dose).

The proposed control strategy is adequate to assure the quality of the product. All impurities associated with the product are known or are part of drug substance structure. Limits proposed for individual impurities and potential leachable compounds were discussed with Pharm. Tox. reviewer. No safety concerns were identified. Please refer to M. Ramasamy's drug product review dated 3/14/19 for additional information.

*Risk Assessment:* CMC Reviewer's risk assessment for critical attributes is shown at the end of the review. In conclusion, the final quality risk is low for the proposed product. No further mitigation necessary (Attachment 1).

*Environmental assessment*: The applicant sought exemption from environmental impact analysis per 21CFR 25.31(a) as the action on this NDA does not increase the use of glucagon. Dr. M. Ramaswamy reviewed the request and granted categorical exclusion from submitting environment assessment. Please refer to M. Ramasamy's drug product review dated 3/14/19 for additional information.

*Expiration Date & Storage Conditions:* The application contains 6 month accelerated stability (40°C/75% RH), 12-18 moths of intermediate and long-term storage stability data (25°C/60% RH, 30°C/65% RH, 30°C/75% RH) for 3 primary stability batches. Stability information was reviewed by drug product reviewer. Drug product review concluded that the product is relatively stable. An expiration period of 18 months is granted when stored at (b) (4) 30°C for the combination product packaged in shrink-wrapped secondary packaging. Please refer to drug product review dated 3/14/19 in Panorama for additional information.

*Container and Carton Label Review:* Drug product reviewer completed review of container and carton label. Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to drug product review for a copy of the label (Attachment 2).

The components of the delivery device (b) (4) are supplied by (b) (4). Secondary packaging unit (tube with (b) (4) desiccant) is supplied by (b) (4). The letters of authorization from the (b) (4) and (b) (4) to access CMC information are provided in their Type III DMFs and the NDA. These DMF were reviewed for material and dimension control information provided in the DMF.

A separate device specific review is performed by CDRH review, which evaluates the device aspects of the product provided in Module 3 Section 3.2.R.3 including reliability studies. Product quality aspects of this combination product including stability data are covered by the CDER drug product review.

## OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, facilities, microbiology, environmental analysis, container and carton label. *OPQ overall recommendation for NDA 210134 is approval.*

***Muthukumar Ramaswamy, Ph.D. 3/15/2019***

***Application Technical Lead Name and Date:***

# ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA

## RISK ASSESSMENT FOR NASAL GLUCAGON POWDER

| *From Initial Risk Identification* | | | *Review Assessment* | | |
|---|---|---|---|---|---|
| ***Attribute/ CQA*** | ***Factors that can impact the CQA*** | ***Initial Risk Ranking*** | ***Risk Mitigation Approach*** | ***Final Risk Ranking*** | ***Lifecycle Considerations/ Comments*** |
| Drug content per actuation | Formulation, Process (fill weight), container/delivery device. / stability/Method | H | (b) (4) | Acceptable | None/Lilly agreed to re-evaluate and update the specifications, as appropriate, for glucagon content and delivered dose uniformity to reflect commercial drug product performance. This analysis will be performed after completion of the release testing of at least 10 post-action production batches and after completion of the stability studies through 24 months (b) (4) for the first three post-action production batches. |
| Delivered Dose Uniformity | Formulation, Process (fill weight), Container closure/delivery device/stability/Method | H | | Acceptable | |
| Shot weight | Solubility, Formulation, Process (fill weight), Container closure/delivery device/Method | H | | Acceptable | None |
| Plume Geometry | Formulation/delivery device/process (bulk density) | M | | Acceptable | None/ Lilly agreed to collect and submit Spray Pattern and Plume Geometry data for the next 6 commercial scale batches post approval. Spray pattern data comparisons with representative clinical batches will be provided at that time. |
| Spray Pattern | Formulation/delivery device/process (bulk density | M | | Acceptable | |
| Particle Size Distribution | Formulation, Process, delivery device | M | | Acceptable | none |
| Impurities/ degradants | Formulation, stability, Process, Container closure & secondary packaging | H | | Acceptable | none |
| Appearance | Formulation, Process, Container closure, stability | H | | Acceptable | none |

| | | | | | |
|---|---|---|---|---|---|
| Microbial load | Container closure<br>Process (b) (4) | H | (b) (4) | Acceptable | none |
| Foreign Particulate matter | Formulation, container /closure/device components | H | | Acceptable | none |
| pH | Formulation | M | | Acceptable | none |
| Leachable/ extractables | Formulation, Process, Container closure, storage conditions | L | | Acceptable | none |
| β-Cyclodextrin Content | Solubility, Formulation, Process (fill weight), container/delivery device | M | | Acceptable | none |
| Dodecyl phosphocholine Content | Solubility, Formulation, Process (fill weight), container/delivery device | M | | Acceptable | none |

# LABELING

## I. Package Insert

### 1. *Highlights of Prescribing Information*

| Item | Information Provided in NDA |
|---|---|
| Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2)) | |
| Proprietary name and established name | Baqsimi and Glucagon |
| Dosage form, route of administration | Powder, nasal |
| Controlled drug substance symbol (if applicable) | none |
| Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8)) | |
| Summary of the dosage form and strength | Powder; 3mg/actuation |

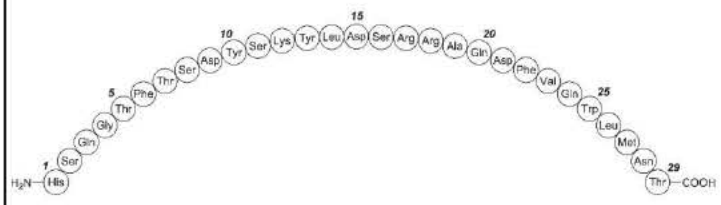
### 2. *Section 2 Dosage and Administration*

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12)) | |
| Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents) | none |

### 3. *Section 3 Dosage Forms and Strengths*

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(4)) | |
| Available dosage forms | |
| Strengths: in metric system | 3mg/actuation |
| Active moiety expression of strength with equivalence statement (if applicable) | glucagon |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | White (b) (4) powder |

### 4. *Section 11 Description*

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)) | |
| Proprietary name and established name | Baqsimi and glucagon |
| Dosage form and route of administration | Powder, nasal |
| Active moiety expression of strength with equivalence statement (if applicable) | 3mg |
| For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>) | Each 3mg dose of drug product contains beta-cyclodextrin, and dodecylphosphocholine. |
| Statement of being sterile (if applicable) | |
| Pharmacological/ therapeutic class | hormone |
| Chemical name, structural formula, molecular weight | Glucagon; 29 amino acid synthetic peptide. Molecular Formula: $C_{153}H_{225}N_{43}O_{49}S$.<br>Molecular weight: 3483g/mol (anhydrous).<br>  |
| If radioactive, statement of important nuclear characteristics. | Not applicable |
| Other important chemical or physical properties (such as pKa or pH) | Drug product powder freely soluble in acidic pH. |

5. ***Section 16 How Supplied/Storage and Handling***

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(17)) | |
| Strength of dosage form | 3mg/actuation |
| Available units (e.g., bottles of 100 tablets) | Single dose unit vial |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | NDC #/ Barcode |
| Special handling (e.g., protect from light) | Store the product in shrink-wrapped tube until ready to use. If tube is open and exposed to moisture performance is not assured. |
| Storage conditions | (b) (4) |
| Manufacturer/distributor name (21 CFR 201.1(h)(5)) | Eli Lilly Inc. |

**Reviewer's Assessment of Package Insert:** Adequate with comments
Labeling comments are finalized during multi-disciplinary team review managed by OND.

Per USP <5> glucagon nasal powder is the non-proprietary name for this product.

Proprietary Name/Established Name: Adequate.

Section 3 Dosage Form and Strength: Adequate. BAQSIMI should be given in one nostril and should not be inhaled.

Section 16.2 - Storage and Handling - Adequate

## II. Labels:

***Container Label***

(b) (4)

***Tube Label***

(b) (4)

***Carton Label***

(b) (4)

| Item | Information provided in the container label | Information provided in the carton label(s) |
|---|---|---|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | Baqsimi (Glucagon nasal powder) | Baqsimi (Glucagon nasal powder) |
| Dosage strength | 3mg | 3mg |
| Net contents | Yes | Yes |
| "Rx only" displayed prominently on the main panel | Yes | Yes |
| NDC number (21 CFR 207.35(b)(3)(i)) | Yes | Yes |
| Lot number and expiration date (21 CFR 201.17) | Yes | Yes |
| Storage conditions | Store the product (b) (4) | (b) (4) |
| Bar code (21CFR 201.25) | | |
| Name of manufacturer/distributor | Yes | Yes |
| And others, if space is available | -- | --- |

**Reviewer's Assessment of Labels:** *Adequate*
*Dosage form, strength, established name, and storage conditions are adequately described in the carton and container label.*

***List of Deficiencies: None***

***Overall Assessment and Recommendation: Adequate***

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Muthukumar Ramaswamy

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Danae Christodoulou

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