CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208232Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 23, 2020

To: Sonia D. Doi, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Jennifer Johnson, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for MYCAPSSA (octreotide) delayed-release capsules, for oral use

NDA: 208232

In response to DMEP's consult request dated May 20, 2020, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and Patient Package Insert (PPI) for MYCAPSSA (octreotide) delayed-release capsules, for oral use. This is a New Drug Application.

PI, IFU, PPI: OPDP's comments on the proposed PI are based on the draft materials sent by DMEP on June 12, 2020 and are provided below.

Please note that comments on the PPI and IFU will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 22, 2020
To:	Jennifer Johnson Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	MYCAPSSA (octreotide)
Dosage Form and Route:	delayed-release oral capsules
Application Type/Number:	NDA 208232
Applicant:	Camargo Pharmaceutical Services, LLC

1 INTRODUCTION

On December 24, 2019, Camargo Pharmaceutical Services, LLC submitted for the Agency's review a Class 2 Resubmission for New Drug Application (NDA) 208232 for MYCAPSSA (octreotide) after a Complete Response Letter dated April 15, 2016 for deficiencies related to Active Pharmaceutical Ingredient manufacturing and the clinical program. This NDA proposes an indication for long-term maintenance treatment of patients with acromegaly.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology on May 18, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MYCAPSSA (octreotide) delayed-release oral capsules.

2 MATERIAL REVIEWED

- Draft MYCAPSSA (octreotide) PPI and IFU received on December 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2020.
- Draft MYCAPSSA (octreotide) Prescribing Information (PI) received on December 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 12, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 DISCUSSION

DMPP extracted the IFU information from the PPI and created a separate document because the purpose of the PPI is to provide information about the prescribed medication and the purpose of the IFU is to provide information about the safe and effective use of the product. Hence, the two documents were reviewed separately.

5 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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06/22/2020 03:15:27 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 9, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 208232
Product Name and Strength:	Mycapssa (octreotide) capsule, 20 mg
Applicant/Sponsor Name:	Chiasma, Inc
OSE RCM #:	2015-1500-3
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 5, 2020 for Mycapssa. The Division of General Endocrinology requested that we review the revised container labels and carton labeling for Mycapssa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made by the Office of Pharmaceutical Quality to update the strength and storage statements.

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: May 27, 2020 **Date consulted:** 4/24/2020

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Division of General Endocrinology (DGE)

Drug: Mycapssa (octreotide) delayed-release capsules for oral use

NDA: 208232

Applicant: Chiasma Inc.

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Indication: For long-term maintenance treatment in acromegaly patients who responded to and tolerated treatment with (b) (4)

Materials Reviewed:

- December 26, 2019 Resubmission, Original
- April 24, 2020, DGE consult, DARRTS Reference ID 4597722
- December 19, 2019 Bynfezia Pen review by Carrie Ceresa, Pharm D., MPH in DARRTS, Reference ID 4535605[1]
- August 22, 2016 Sandostatin LAR review by Jane Liedtka, MD in DARRTS, Reference ID:3974934[1]

Consult Question: "Review of the labeling for PLLR compliance, and any additional labeling recommendations from the Maternal Health Team to ensure the safe use of Mycapssa (octreotide) delayed-release capsules"

[1] The Bynfezia and Sandostatin LAR consult reviews were part of the materials reviewed for the background section but were not a source relied upon for the labeling recommendations for this consult. Rather, the cross-reference to the Bynfezia and Sandostatin LAR consults are included to avoid duplicating background information relevant to this class of products

INTRODUCTION

On December 26, 2019, the applicant, Chiasma, resubmitted NDA 208232 for Mycapssa (octreotide) delayed-release capsules for oral use for long-term maintenance treatment in acromegaly patients who responded to and tolerated treatment with (b) (4)
The package insert is to comply with the Pregnancy and Lactation Labeling Rule (PLLR) requirements. The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on April 24, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Regulatory History

Mycapssa (octreotide) was originally submitted to the FDA on June 12, 2015, under the 505(b)(2) pathway, for long-term maintenance treatment of patients with acromegaly. The drug relied upon is Sandostatin (octreotide acetate) injection immediate-release (IR), NDA 019667.

On April 15, 2016, the applicant (Chiasma) received a Complete Response (CR) notification because:

1. During a recent inspection of (b) (4) located at (b) (4) our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application can be approved.
2. The data in the application do not provide substantial evidence that Mycapssa is effective as the effect captured in study CH-ACM-01 cannot be purported to represent the effect of Mycapssa. Satisfactory resolution of this deficiency is required before this application can be approved.

On December 26, 2019, the applicant submitted the current submission, a resubmission for NDA 208232 as a response to the CR.

Drug Characteristics[2]

Table 1: Drug Characteristics

Drug Class	A somatostatin analog
Mechanism of Action	Octreotide displays a high affinity for somatostatin receptor subtypes 2 and 5. Octreotide exerts pharmacologic actions similar to the natural hormone somatostatin, but is a more potent inhibitor of GH, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH), decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.
Molecular Weight	1019.3 Daltons
Form	The acetate salt of a cyclic octapeptide
Protein Binding	65% bound to plasma proteins
Terminal Half-Life	2-3.5 hours
Bioavailability	Absolute bioavailability of about 76-80% following oral dose

[2] Applicant's proposed Mycapssa Product Insert/Labeling of December 26, 2019

REVIEW
PREGNANCY
Acromegaly and Pregnancy[3]

- Acromegaly is a rare disorder caused by overproduction of growth hormone (GH) which is produced by the pituitary gland. The increase in growth hormone is typically caused by a benign, noncancerous tumor of the pituitary.[4]
- The median age at diagnosis is the fourth and fifth decade of life (males ages 36 to 48 and females ages 38 to 56).[5]
- Due to changes in growth hormone and insulin like growth factor-1 it is difficult to diagnosis acromegaly in pregnancy.[6]
- Acromegaly does not appear to cause adverse maternal or fetal outcomes during pregnancy. It is also recommended to consider pituitary surgery during pregnancy to prohibit tumor enlargement.[5]
- Although fertility is frequently impaired,[7] pregnancy is apparently becoming more common due to improvement in acromegaly treatment, as well as infertility therapies.
- As both acromegaly and pregnancy are associated with hypertension and diabetes, in uncontrolled acromegalic patients, pregnancy is reported to increase the prevalence of those comorbidities and potentially complicate obstetrical/fetal outcomes.[8]

Nonclinical Experience

The applicant is relying on previous nonclinical findings of safety for the drug relied upon Sandostatin Injection (octreotide acetate for injection), which was approved under NDA 019667. No embryonic and fetal development toxicity studies with Mycapssa have been conducted in animals. Reproduction studies performed in rats and rabbits with injectable octreotide acetate revealed no evidence of fetal harm at doses expected to result in exposure levels up to 16 times higher than those expected in patients at the highest recommended dose of MYCAPSSA (based on octreotide acetate injection body surface area). No fertility studies in animals have been conducted with MYCAPSSA. For extensive nonclinical review, the reader is referred to the review by Jessica Hawes, Ph.D. in DARRTS, February 23, 2016 and Reference ID: 3891521.

Review of Literature
Applicant's and DPMH Review of Literature
The applicant has not identified any recent publications. DPMH conducted a search of published literature using PubMed and Embase regarding octreotide, somatostatin, somatostatin analogs from 2018 to today and exposure during pregnancy. No new publications for octreotide use in pregnancy have been identified by either the applicant or this reviewer. Therefore, no new safety

[3] The Bynfezia and Sandostatin LAR consult reviews were part of the materials reviewed for the background section but were not a source relied upon for the labeling recommendations for this consult. Rather, the cross-reference to the Bynfezia and Sandostatin LAR consults are included to avoid duplicating background information relevant to this class of products
[4] Acromegaly. National Institute of Health. National Institute of Diabetes and Digestive and Kidney Diseases. https://www niddk.nih.gov/health-information/endocrine-diseases/acromegaly.
[5] Lavrentaki, A et al. Epidemiology of acromegaly: review of population studies. Pituitary. 2017. 20(1): 4-9
[6] Laway B, 2015, Pregnancy in acromegaly. Ther Adv Endrocrinol Metab, 6(6):267-272.
[7] Grynberg M et al. Female gonadal function before and after treatment of acromegaly. Journal of Clinical Endocrinology and Metabolism 2010 95 4518–4525.
[8] Caron P et al. Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women. Journal of Clinical Endocrinology and Metabolism. 2010; 95: 4680–4687.

concerns were identified. Octreotide crosses the human placenta to the fetus.[9] For extensive review of the literature, the reader is referred to the Bynfezia and Sandostatin LAR reviews.[1,3]

Review of Pharmacovigilance Database (PV) and Utilization

The drug has not yet been approved and therefore, it is not marketed in the US or elsewhere. There are no PV data nor utilization data.

As per applicant,

> There are no controlled studies in pregnant women. In post-marketing data for somatostatin analogs, a limited number of exposed pregnancies has been reported in patients with acromegaly treated with injectable octreotide (reported in the literature). Most women were exposed to octreotide acetate during the first trimester of pregnancy at doses ranging from 100–300 mcg/day of octreotide acetate subcutaneously (SC); however, some women elected to continue octreotide acetate therapy throughout pregnancy. In cases with a known outcome, no congenital malformations were reported.

Summary

In animal reproduction studies, no adverse developmental effects were observed with intravenous administration of octreotide to pregnant rats and rabbits during organogenesis. The clinical data from published literature regarding pregnancy exposure to injectable octreotide have not identified a pattern of malformations or an increased risk of miscarriage, and adverse maternal or fetal outcomes.

There are no new safety concerns to communicate in pregnancy labeling.

Additionally, DPMH is recommending a Post-Marketing Requirement (PMR) for a single arm pregnancy safety study (SPSS). The rationale for this PMR is that females of reproductive potential are anticipated to use the drug and the available pregnancy data are not sufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. More information is needed to guide safe use of Mycapssa during pregnancy. As a rare disorder, the small population is unlikely to allow adequate enrollment numbers for a pregnancy registry and a complementary study to be interpretable. Therefore, an SPSS (which does not require an internal control group or inferential statistical analysis) is being recommended.

LACTATION

Nonclinical Experience

Clinical lactation studies with octreotide have not been conducted. Octreotide administered subcutaneously passes into the milk of lactating rats. Following a subcutaneous dose (1 mg/kg) of octreotide to lactating rats, transfer of octreotide into milk was observed at a low concentration compared to plasma (milk/plasma ratio of 0.009).

Review of Literature

Applicant's and DPMH Review of Literature

The applicant did not identify any new publications. DPMH conducted a search of published literature using PubMed and Embase, LactMed, Drugs in Pregnancy and Lactation by Briggs and Freeman and Medications and Mothers' Milk by Thomas Hale regarding octreotide and lactation. There is no data on the presence of octreotide in human milk. Hale in Medications and Mothers' Milk states that due to its molecular weight, transfer to milk is probably minimal. This product, if present in milk, would

[9] Briggs G and R Freeman. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Wolters Kluwer/Lippincott Williams and Wilkins. http://ovidsp.dc2.ovid.com/sp-4.02.1a/ovidweb.cgi

not likely be absorbed to any degree. Listed as "Probably Compatible", Hale also recommends that infants who are breastfed are monitored for vomiting, diarrhea and changes in feeding.

Review of Pharmacovigilance Database
There are no reports of octreotide exposure during breastfeeding.

Summary on Lactation
Octreotide administered subcutaneously passes into the milk of lactating rats. Following a subcutaneous dose (1 mg/kg) of octreotide to lactating rats, transfer of octreotide into rat milk was observed at a low concentration compared to plasma (milk/plasma ratio of 0.009). If the drug is present in animal milk, it is likely present in human milk but due to species-to-species differences in lactation physiology, the concentration in animal milk does not necessarily predict the concentration of drug in human milk. There are no data on the presence of octreotide in human milk; however, due to octreotide's high molecular weight, if it was present in human milk, then it would likely be present in low amounts. DPMH recommends the use of the benefit/risk statement in subsection 8.2 of the Mycapssa labeling.
Additionally, DPMH is recommending a PMR milk-only clinical lactation study for Mycapssa because females of reproductive potential are anticipated to use the drug and there is no data on the presence of drug in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. If the drug is found to be present in maternal milk, then the applicant should see if the drug is absorbed by the breastfed infant.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical experience
Injectable octreotide acetate did not impair fertility in rats at exposures 7 times higher than those expected in patients at the highest recommended dose of Mycapssa.

Review of Literature
Applicant's and DPMH Review of Literature
The applicant did not identify any new publications. DPMH conducted a search of published literature in PubMed and Embase regarding octreotide and its effects on fertility. No new publications were identified. The reader is referred to the review of Sandostatin LAR by Jane Liedtka, M.D.[2]
In general, acromegaly may lead to infertility. It appears that menstrual irregularity is common in women with acromegaly (81% of patients) in Kaltsas *et al*[10] publication. Octreotide normalizes insulin-like growth factor 1 (IGF-1) and growth hormone (GH) and because of this effect increases the risk of pregnancy. Female patients of childbearing potential should be advised to use effective contraception during treatment with octreotide. Also, at risk for pregnancy are women with polycystic ovarian syndrome (PCOS) which responds well to octreotide (off label use). Women with PCOS experience elevated fasting and glucose stimulated insulin levels, decreased IGF-binding proteins and hirsutism, which all respond well to octreotide.[11] These events may improve in PCOS patients under treatment with octreotide and lead to unintended pregnancy.

[10] Kaltsas GA et al. Menstrual Irregularity in Women with Acromegaly. The Journal of Clinical Endocrinology & Metabolism. 1999. 84; 2731-2735.
[11] Anthony L et al. Review From somatostatin to octreotide LAR: evolution of a somatostatin analogue. Current Medical Research & Opinion.2009; Vol. 25, No. 12: 2989-2999.

Summary
Octreotide did not impair fertility in rats. Evidence outlined in this review, though not conclusive, suggests there is a low likelihood of congenital malformations associated with exposure to octreotide during pregnancy. Therefore, there is no need for pregnancy testing prior to initiating treatment with Mycapssa. Counseling regarding the potential for unintended pregnancy in premenopausal females should be advised, as the therapeutic benefits of octreotide to reduce GH levels and normalize IGF-1 concentration may lead to improved fertility.

DISCUSSION
DPMH recommends PMRs for a single arm pregnancy safety study (SPSS) and a milk-only clinical lactation study for Mycapssa because females of reproductive potential are anticipated to use the drug and there is little or no relevant data available from the human experience. In an email exchange with the DGE clinical team, a rationale was provided why the Division does not recommend proceeding with the above mentioned PMRs. DGE clinical team concludes that "[Acromegaly] is an orphan population and there are not enough patients who become pregnant. By Endocrine Society guidelines it is recommended to stop all treatment when pregnancy occurs - the tumors usually do not grow during the pregnancy. During lactation similar action can be taken- to stop the drug."

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2, 8.3 and 17 of Mycapssa labeling for compliance with the PLLR (see below). On May 26, 2020, DPMH presented labeling recommendations to the Division. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy (8.3)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from case reports with octreotide acetate use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with MYCAPSSA. No adverse developmental effects were observed with intravenous administration of octreotide to pregnant rats and rabbits during organogenesis at doses 7 and 13 times, respectively, the clinical dose based on octreotide injection body surface area. Transient growth retardation, with no impact on postnatal development, was observed in rat offspring from a pre- and post-natal study of octreotide at intravenous doses below the clinical dose based on octreotide injection body surface area *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous doses of octreotide up to 1 mg/kg/day during the period of organogenesis. A slight reduction in body weight gain was noted in pregnant rats at 0.1 and 1 mg/kg/day. There were no maternal effects in rabbits or embryo-fetal effects in either species up to the maximum dose tested. At 1 mg/kg/day in rats and rabbits, the dose multiple was approximately 7 and 13 times, respectively, the clinical dose based on octreotide injection body surface area.
In a pre- and post-natal development rat study at intravenous doses of 0.02-1 mg/kg/day, a transient growth retardation of the offspring was observed at all doses which was possibly a consequence of growth hormone inhibition by octreotide. The doses attributed to the delayed growth are below the clinical dose based on octreotide injection body surface area.

8.2 Lactation
Risk Summary
There is no information available on the presence of octreotide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Studies show that octreotide administered subcutaneously passes into the milk of lactating rats *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's

clinical need for MYCAPSSA, and any potential adverse effects on the breastfed child from MYCAPSSA or from the underlying maternal condition.

Data
Following a subcutaneous dose (1 mg/kg) of octreotide to lactating rats, transfer of octreotide into milk was observed at a low concentration compared to plasma (milk/plasma ratio of 0.009).

8.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as the therapeutic benefits of a reduction in GH levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in acromegalic females treated with octreotide may lead to improved fertility.

17 PATIENT COUNSELING INFORMATION
Females and Males of Reproductive Potential
Inform female patients that treatment with Mycapssa may result in unintended pregnancy *[see Use in Specific Populations (8.3)]*.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 26, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 208232
Product Name and Strength:	Mycapssa (octreotide) capsule, 20 mg
Applicant/Sponsor Name:	Chiasma, Inc
OSE RCM #:	2015-1500-2
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 18, 2020 for Mycapssa. The Division of General Endocrinology requested that we review the revised container labels and carton labeling for Mycapssa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton and container labels are acceptable from a medication error perspective and we have no additional recommendations at this time.

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[a] Fanari, M. Label and Labeling Review for Mycapssa (NDA 208232). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 April 8. RCM No.: 2015-1500-1.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 8, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208232
Product Name and Strength:	Mycapssa (octreotide) capsule, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chiasma, Inc
FDA Received Date:	December 26, 2019
OSE RCM #:	2015-1500-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the class 2 resubmission for Mycapssa (octreotide) capsule, the Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed Mycapssa Prescribing Information (PI), Prescribing Patient Information (PPI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), Prescribing Patient Information (PPI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Use of symbols (e.g., “+”).	Symbols may lead to confusion or be mistaken as opposite of intended.	Replace the symbols “+” with the intended meaning to prevent misinterpretation and confusion.

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	A statement that Mycapssa should be swallowed whole is missing.	Prevent incorrect manipulation of the capsule which could lead to decreased efficacy.	Include "Mycapssa capsules should be swallowed whole and should not be crushed or chewed" or a similar statement in this section. This information is listed in Section 17 Patient Counseling Information.
2.	Multiple dosing recommendations described in bullet format.	Improve readability.	Consider displaying recommended dosing in a chart format.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section lacks information about capsule imprinting, shape, and color.	Facilitate product identification in case of mix-up.	We recommend adding a description of the capsule to include imprint code, shape and color to the How Supplied/Storage and Handling section.
2.	NDC number denoted by a placeholder.	Facilitate product identification.	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type. The NDC number should be updated to reflect the actual numerical NDC number.
Patient Prescribing Information			
1.	The "How should I take Mycapssa?" section contains the statement (b) (4) (b) (4)	Based on post-marketing reports negative statements (b) (4) may have the opposite of the intended meaning because the word (b) (4) can be overlooked and the warning can be	Remove the statement (b) (4) (b) (4)

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		misinterpreted as an affirmative action.	
2.	Figure B is not located after the corresponding statement which refers to it.	Improve proper use of product.	Relocate Figure B so that it is located directly below the Step "Place the tip of a thumb at the edge of a capsule's plastic cavity".
3.	Images in Figure A could benefit from further differentiation.	Improve proper use of product.	Consider the use of color for images in Figure A to improve visibility and differentiation of the steps for opening the wallet and removing the capsule.

Table 3. Identified Issues and Recommendations for Chiasma, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
ALL Carton Labeling and Container Labels			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are

Table 3. Identified Issues and Recommendations for Chiasma, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Label (medication card)			
1.	Product strength per single unit statement is missing.	To avoid wrong dose errors and to clarify the designated strength is per unit.	Add the following statement on both panels (left and right) of the medication card: "Each capsule contains XX mg octreotide".
2.	The proprietary name, established name, and strength of the product are not prominent and displayed in a vertical orientation.	Improve user readability and product identification.	Increase the font size and prominence of the proprietary name, established name, and strength of the product. In addition, consider rotating the proprietary name, established name and strength displayed from a vertical orientation to a horizontal to improve user readability orientation.
3.	Product name and strength are only on one panel (blue).	Facilitate product identification, especially in the event that the two panels (blue and white) are separated.	Consider including the proprietary name, established name, and strength of the product on both panels (left and right).
4.	How to administer product statement only present on one panel (blue) of medication card.	Improve proper product administration.	Consider adding the statement "Always take with a glass of water on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal" to both panels (left and right) of the medication card.

Table 3. Identified Issues and Recommendations for Chiasma, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
5.	(b) (4) (b) (4)	Adds to visual clutter and potential misinterpretations.	Remove the (b) (4) (b) (4)
Carton Labeling (wallet pack)			
1.	Product strength statement is missing.	Facilitate product identification.	The product strength statement should be added after the proprietary name and established name.
2.	NDC number denoted by a placeholder. Therefore, we were unable to assess the appropriateness of the NDC numbers from a medication safety perspective.	Facilitate product identification.	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type. The NDC number should be updated to reflect the actual numerical NDC number.
3.	Usual dosage statement requires revisions.	Per 21 CFR 201.100 (b)(2).	Revise the reference to prescribing information statement to read as follows: "Recommended Dosage: See prescribing information."
4.	Opening instructions are not prominent.	Increase visibility and use readability.	Increase the font size of the Opening Instructions.
5.	(b) (4)	Redundant information and reduce visual clutter.	Consider removing the statement (b) (4) (b) (4)
6.	Use of the term (b) (4) instead of	Revising the term (b) (4) to read "left thumb" will harmonize the	Consider revising the (b) (4) (b) (4) Step 1 section to read as follows:

Table 3. Identified Issues and Recommendations for Chiasma, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	"left thumb" in step 1 of opening instructions.	Opening Instructions with the Instructions for Use.	(b) (4)

4 CONCLUSION

Our evaluation of the proposed Mycapssa Prescribing Information (PI), Prescribing Patient Information (PPI), container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Error! Reference source not found.Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Chiasma, Inc so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Mycapssa received on December 26, 2019 from Chiasma, Inc, and the listed drug (LD).

Table 4. Relevant Product Information for Mycapssa and the Listed Drug		
Product Name	Mycapssa	Sandostatin[a]
Initial Approval Date	N/A	1988
Active Ingredient	octreotide	Octreotide acetate
Indication	Long term maintenance treatment in acromegaly patients (b) (4) (b) (4)	Reduce blood levels of growth hormone and IGF-I in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptne mesylate
Route of Administration	Oral	Subcutaneous or intravenous
Dosage Form	Capsule	injection
Strength	20 mg	Ampules: 50 mcg/mL, 100 mcg/mL and 500 mcg/mL Multi-Dose Vials: 1000 mcg/5 mL (200 mcg/mL) and 5000 mcg/5 mL (1000 mcg/mL)
Dose and Frequency	- Initial dose of 20 mg BID given orally (20 mg morning and 20 mg evening) - Dosage may be increased to 60 mg daily (40 mg morning and 20 mg evening) if IGF-1 levels increase, as determined by the physician. - If clinically necessary, may increase the dose to 80 mg	Initiate at 50 mcg three times a day. Dose may be increased up to 500 mcg three times daily.

[a] Sandostatin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Apr 11 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019667s067lbl.pdf.

	daily (40 mg morning and 40 mg evening)	
How Supplied	- Wallet pack with medication card containing 28 capsules	Ampules: 50 mcg/mL, 100 mcg/mL and 500 mcg/mL Multi-Dose Vials: 1000 mcg/5 mL (200 mcg/mL) and 5000 mcg/5 mL (1000 mcg/mL)
Storage	- Until first use, store unopened wallets at 36° to 46°F (2° to 8°C). Do not freeze. - After first use, opened wallets may be stored at 68° to 77°F (20° to 25°C) for up to 1 month.	Store refrigerated at 36°F to 46°F (2°C to 8°C) and protect from light. Stable at room temperature 70°F to 86°F (20°C to 30°C) for 14 days if protected from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 27, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Mycapssa. Our search identified one previous review[b] , and we identified that our previous recommendations where not conveyed to the Applicant. We evaluated the previous recommendations to determine if they are still relevant and have incorporated those relevant to this review in sections 3 above.

[b] Ayres, E. Label and Labeling Review for Mycapssa (NDA 208232). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 18. RCM No.: 2015-1500.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Mycapssa labels and labeling submitted by Chiasma, Inc.

- Container Label (medication card) received on December 26, 2019
- Carton Labeling (wallet pack) received on December 26, 2019
- Prescribing Information (see link) received on December 26, 2019 Application 208232 - Sequence 0031 - 11413-draft-labeling-text-WORD
- Patient Prescribing Information (see link) received on December 26, 20109 Application 208232 - Sequence 0031 - 11413-patient-info-WORD

F.2 Label and Labeling Images

Container Label (medication card)

(b) (4)

[redacted]

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINA N FANARI
04/08/2020 05:28:22 PM

SEVAN H KOLEJIAN
04/09/2020 08:55:47 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 5, 2016
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	MYCAPSSA (octreotide)
Dosage Form and Route:	capsules
Application Type/Number:	NDA 208232
Applicant:	Chiasma, Inc.

1 INTRODUCTION

On June 4, 2015, Chiasma submitted for the Agency's review an Original New Drug Application (NDA) for MYCAPSSA (octreotide) capsules indicated for the treatment of acromegaly. On July 22, 2015, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Packet Insert (PPI) and Instructions for Use (IFU) for MYCAPSSA (octreotide) capsules.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPIand IFU for MYCAPSSA (octreotide) capsules.

2 RECOMMENDATIONS

- The proposed patient information is not in the format currently used in patient labeling. The proposed PPI format should follow the 21 CFR 208 guidelines which govern the format of the Medication Guides (MG).
- The proposed patient label appears to be a combination of the PPI and IFU. The applicant should re-submit and clearly identify the patient labeling as either one document, with the PPI followed by the IFU or as two separate documents. As one document the PPI has the IFU appended and the document will be given to the patient either by the pharmacist or packaged in the medication packaging.

3 CONCLUSIONS

Due to outstanding clinical and statistical deficiencies, DMEP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

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/s/

TWANDA D SCALES
04/05/2016

MARCIA B WILLIAMS
04/05/2016

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

CLINICAL INSPECTION SUMMARY

DATE: February 5, 2016

TO: Smita Abraham, M.D., Clinical Reviewer
Marina Zemskova, M.D., Medical Team Leader
Jennifer Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

NDA: 208232

APPLICANT: Chiasma, Inc.

DRUG: Octreotide acetate capsules/ MYCAPSSA™

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Long-term maintenance treatment in acromegaly patients (b) (4)
(b) (4)

CLINICAL INSPECTION SUMMARY GOAL DATE: February 15, 2016
PDUFA DATE: April 15, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three foreign clinical sites as well as the Sponsor. The inspection of one clinical investigator listed below revealed regulatory violations. The inspection of the Sponsor also revealed regulatory violations.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity.

The preliminary classification for Dr. Glaser is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application.

The preliminary classification for Drs. Popović and Schopohl is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information.

The preliminary classification for the Sponsor is VAI. Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Data from the Sponsor is considered reliable based on the available information.

Overall, while the inspectional findings based on the inspections of the one clinical site and the Sponsor represent observed regulatory deficiencies, these findings are unlikely to have a significant impact on overall results.

In general, based on the inspections of the three clinical sites and the Sponsor, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

II. BACKGROUND

Chiasma, Inc. (Chiasma) is seeking approval of a new drug application for octreotide capsules for long-term maintenance therapy in acromegaly patients (b) (4) (b) (4) Identifying the need for an alternative to the currently available octreotide injections, Chiasma has developed a new formulation to enable the oral delivery of octreotide acetate. The octreotide capsule product in this application has the proposed trade name of MYCAPSSA™, previously referred to as Octreolin® or oral octreotide acetate (OOA).

Inspections were requested for the following clinical study:

- **CH-ACM-01** Efficacy and Safety of Oral Octreolin™ in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs

This was a pivotal Phase 3, open-label, dose-titration, baseline-controlled, multi-center, international study. A total of 34 sites enrolled at least one patient. There were no US sites.

There were 235 subjects screened, 155 subjects enrolled and 102 subjects who completed the core study. There were 88 subjects that enrolled into the extension study and 82 subjects completed.

Adult patients diagnosed with acromegaly who, at screening, were receiving a stable dose of a parenteral somatostatin receptor ligand (SRL) for at least 3 months and who were considered responders to their therapy were eligible for enrollment in this study.

The primary efficacy endpoint was IGF-1 concentration at the completion of the Core Treatment Period. The primary response measure was defined as insulin-like growth factor-1 (IGF-1) <1.3 times upper limits of normal and mean integrated GH < 2.5 ng/mL over 2 hours.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208232 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

III. RESULTS (by Site):

Name of CI/ Mailing Address/State/Country Site#	**Protocol CH-ACM-01 # of Subjects Randomized**	**Inspection Date**	**Classification**
Vera Popović-Brkic, M.D., Ph.D. Clinical Centre of Serbia 13, Dr Subotica Street 11000 Belgrade Serbia *Mailing address:* Promedis Nebojsina 45 Belgrade, Serbia 11000 Site 1201	11	11/23 – 11/27/2015	No Action Indicated (NAI)
Jochen Schopohl, M.D. Klinikum der Universität München Medizinische Klinik und Poliklinik IV Ziemssenstraße 1 München, Germany 80336 Site 0402	8	11/16 – 11/20/2016	No Action Indicated (NAI)

Benjamin Glaser Hadassah Ein-Karem Medical Center P.O. Box 12000 Jerusalem 91120 Israel Site 0602	6	11/08 – 11/11/2015	Voluntary Action Indicated (VAI)
Chiasma 10 Hartom St. Har Hotzvim Jerusalem Israel 9777510 Sponsor	NA	11/01 – 11/05/2015	Voluntary Action Indicated (VAI)

Key to Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Vera Popović-Brkic/ Serbia/ Site 1201

General observations/commentary: Records were organized and legible. Medical records/source documents were translated by staff from the Medicines and Medical Devices Agency of Serbia. The first subject was consented and screened (b) (6).

There were 17 subjects screened. Four of these 17 subjects were screen failures due to IGF-1 values being higher than permitted. These four subjects were rescreened, three prior to rescreening being specifically permitted in protocol Version 3 (Amendment 2). Rescreening consisted of a second blood draw for lab analysis of IGF-1 during the 4-week screening period. Correspondence in the study records show that the Sponsor granted approval for the rescreening prior to subject rescreening. Subjects rescreened were: (b) (6)
(b) (6)

There were 12 subjects enrolled into the core study (Subject (b) (6) is listed as a screen failure but, more accurately, the subject withdrew consent at Day 0 due to the blood draw requirements; therefore the total enrolled was technically 12 but reported as 11). Seven subjects completed the core study. There were six subjects that enrolled into the extension study and five subjects completed the extension study. All subject records were reviewed, including all screen failures.

The study appeared to be generally conducted in accordance with the protocol. There was one subject that should not have been enrolled. Subject (b) (6) had pituitary surgery on (b) (6). An exclusion criterion in all protocol versions is "pituitary surgery within the prior 6 months". The subject was screened on (b) (6) deemed eligible for study inclusion at baseline on (b) (6) and received study drug on (b) (6) Pituitary surgery was less than 6 months prior to enrollment. The site did take appropriate action when they became aware of the deviation. The Sponsor was contacted and approved continuation of the subject in the trial.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

During the inspection it was noted that the end of the fixed dose period for Subject (b) (6) should be (b) (6) The line listings show the end of the fixed dose period for this subject as (b) (6) During the inspection the Sponsor was contacted. There was a limitation in the electronic case report form (eCRF). The subject received first dose of study drug (b) (6) and had a dose escalation phase which ended (b) (6), which then began the fixed-dose phase (TB1). Subject came in on (b) (6) for Study Visit TB6 (fixed dose, visit 6). However, one more study visit on the fixed dose schedule was needed to complete the protocol required minimum of seven months. When the subject arrived (b) (6) for what was truly the last fixed dose visit, the data had to be entered in the eCRF as an unscheduled visit as there was no TB7/end of treatment visit in the eCRF (system design flaw). During analysis, the statistical program pulled data from the (b) (6) visit instead of the (b) (6) visit. The design flaw only impacted the one subject, (b) (6) at this site. (Whether or not a subject reached more than visit TB6 would depend on how quickly the subject went through the dose escalation phase). Subject (b) (6) was a responder so analysis is not affected.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Jochen Schopohl/ Germany/ Site 0402

General observations/commentary: Records were available, legible and organized. Translation was performed by a staff physician who was not involved with the study. All subject records were reviewed. The first subject was consented and screened on (b) (6)

There were eight subjects screened. Two of the subjects (b) (6) were rescreened per approval of the Sponsor. Eight subjects were enrolled into the core study and six completed the core study. Four subjects enrolled into the extension study and

three completed the study.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

It was noted that this site combined the Baseline and TA1 visits. TA1 is the first visit of the dose escalation phase. This is not prohibited by the protocol and the site had discussed this with the medical monitor prior to implementation.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Benjamin Glaser/ Israel/ Site 0602

General observations/commentary: The source documents/subjects' files were poorly organized; the worksheets and forms were not completely filled out. Some of the laboratory test results were missing and had to be re-printed from the central laboratory during the inspection.

There were six subjects screened and five subjects enrolled into the core study. Four subjects entered the extension study and three subjects completed the study. All subject records were reviewed. The first subject signed consent and began screening on (b) (6) (b) (6)

At noted in the Clinical Study Report, Subject (b) (6) was excluded from the mITT Population because the subject did not have an efficacy assessment post visit TA1 (first dose with study drug).

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the signed investigator statement. Specifically,
    a. Training was not documented for several staff members.
    OSI Reviewer Comment: Dr. Glaser acknowledged that there was no documentation but stated that he personally trained the staff and had staff meetings regularly to go over the protocol and issues.
    b. Subject (b) (6) was enrolled into the extension study without

documentation of eligibility.
OSI Reviewer Comment: The subject was in-fact eligible but the issue was of documentation and poor record keeping. Documents at the site show that the subject entered the Extension Treatment period (b) (6) *; the physical examination was signed off by the sub-investigator* (b) (6) *and the Eligibility Criteria was signed off by the sub-investigator on* (b) (6) *. Dr. Glaser said that he saw the subject* (b) (6) *but the records were misplaced and the sub-investigator refilled out the information again when he saw it missing from the files. The originals were subsequently found.*

c. Subject (b) (6) had an abnormal ECG (first degree block and RBBB) but there was no documentation of any follow-up.
OSI Reviewer Comment: In Dr. Glaser's response, he stated that he follows the subject in his private clinic and saw him (b) (6) *at which time the subject stated he was being followed up by a cardiologist. Dr. Glaser acknowledged that the information should have been documented in the study source records.*

d. Subject (b) (6) had treatment started less than 28 days after the last somatostatin injection. The last somatostatin injection was (b) (6) and the investigational product was taken (b) (6) .
OSI Reviewer Comment: Dr. Glaser acknowledged this oversight. The protocol states "Subjects will begin therapy with Octreolin no earlier than one month following the last injection of a long-acting parenteral somatostatin analog". This was not listed as a protocol deviation in the application as it was not considered a major deviation [Last dose of parenteral somatostatin analog received <3 weeks prior to first dose of study drug].

e. The Medication Diary was filled out by the study coordinator at the visits instead of by the subject per protocol.
OSI Reviewer Comment: Dr. Glaser stated that subjects often forgot to fill out their diaries and the study coordinator would sit with the subject during the visit and fill it out based on the subjects' input.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,
    a. Physical exams were not always documented as being performed
    b. The determination of clinical significance for laboratory results was not consistent across subject files.
    c. There were some minor inconsistencies with the source records due to sloppiness
    OSI Reviewer Comment: The worksheets had some ambiguous language that was confusing to the staff, including asking if a symptom-directed PE was performed. If the PE was not symptom-directed, they were not sure how to respond. There were also other CRFs submitted which documented some of the exams.

3. Investigational drug disposition records are not adequate with respect to dates,

quantity, and use by subject. Specifically,

a. Study drug compliance could not be assessed accurately as the subjects did not fill out the medication diaries (they were completed by the Study Coordinator when the subject returned for their study visit and not by the subjects at time of dosing), source case report forms were not always completed, and drug accountability logs were not properly completed.
OSI Reviewer Comment: Treatment compliance was to be assessed at all visits based on drug accountability (capsule count) and subject's diary review. At noted earlier, the study coordinator often sat with the subject and filled out the medication diary. Dr. Glaser acknowledged that the drug accountability forms were not consistently completed, making reconciliation difficult. The study coordinator gave the returned medication to the pharmacist, who maintained his own records in the pharmacy binder with recordings of drug returned, drug dispensed and drug re-dispensed. Using this information, Dr. Glaser stated that drug accountability is much more accurate.

b. Some subjects were given re-dispensed medication after the labelled drug expiration date.
OSI Reviewer Comment: Subjects were instructed to take re-dispensed medication first but some did not. Dr. Glaser pointed out in his response the updated stability data with an extended shelf life that was within the dosing times.

OSI Reviewer Comment: Dr. Glaser responded to the 483 observations on November 26, 2015 and submitted corrective actions. His response was determined to be acceptable.

Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Chiasma/ Israel

General observations/commentary: Chiasma is a US Corporation in Newton, MA with an Israel subsidiary. The inspection focused on organizational structure and personnel, staff responsibilities, transfer of obligations, communications with contractors and oversight, contracts, SOPs, DMC formation and committee member agreements, 1572s, financial disclosure, training, data management, drug accountability, monitoring, and all site documents pertaining to the sites inspected.

Prior to initiation of the study, Chiasma assessed the sites to determine if they were qualified for the study. The monitoring was initially conducted by the CRO (b) (4) for the European sites and later it was also contracted to the CRO (b) (4) also (b) (4) CRO was sub-contracted by (b) (4) to do monitoring. (b) (4) was also contracted

by Chiasma for [redacted] (b) (4), (b) (4)

[redacted] (b) (4) was responsible for collecting Financial Disclosures and ensuring they were updated accordingly. Financial Disclosures were not always submitted to reflect the changes in the financial situation of the investigator.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

[redacted] (b) (4)

OSI Reviewer Comment: Chiasma submitted a response November 24, 2015 to the 483 observations with acknowledgement of the observations and the corrective actions that have been put into place to prevent reoccurrences. The response was determined to be acceptable.

Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to

significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 18, 2015
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208232
Product Name and Strength:	Mycapssa (octreotide) capsule, 20 mg
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Chiasma, Inc
Submission Date:	June 15, 2015
OSE RCM #:	2015-1500
DMEPA Primary Reviewer:	Ebony Ayres, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Associate Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Mycapssa (octreotide) capsules, 20 mg (NDA 208232) for areas of vulnerability that may lead to medication errors. The Division of Metabolism and Endocrinology Products (DMEP) requested this review as part of their evaluation of the 505(b)(2) submission for Mycapssa. The reference listed drug Sandostatin (octreotide acetate, NDA 019667) was approved in October 1988.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed labels, labeling, and prescribing information (PI) for Mycapssa, NDA 208232. Mycapssa is the first oral dosage form of octreotide and is intended for the long term maintenance treatment of acromegaly. Currently, octreotide is only available in parenteral dosage forms for intravenous, subcutaneous, and intramuscular use.

Our review of the proposed PI found that the dosing information is not displayed in a consistent manner. The initial dosing is listed as milligrams per dose (e.g., 20 mg two times a day), whereas subsequent dosing information is listed as milligrams per day (e.g., 60 mg daily). Discordance in the display of dosing information may lead to misinterpretation and dosing errors. The use of tabular or bullet point display of the dosing information may also help to ensure clarity and selection of the correct dose. Additionally, the PI can be improved to include information regarding the appearance of the capsule and proper handling to facilitate product identification and safe use, respectively.

The container label and carton labeling can be revised to increase prominence and clarity of important prescribing information, such as proprietary name and strength. We further note that the container label can be improved to increase the prominence of statements indicating that Mycapssa must be taken on an empty stomach is necessary, as the extent of Mycapssa's absorption is significantly decreased when taken with food.

Additionally, the Instructions for Use can be improved to provide additional clarity and eliminating unnecessary information. We defer to Division of Medical Policy Programs (DMPP) to provide additional recommendations for the Instructions for Use.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the labels and labeling that can be revised to increase clarity, improve readability, and add important critical information to help mitigate medication errors. We provide recommendations in Section 4.1 and 4.2 below. We advise the following recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Mycapssa Prescribing Information
    a. Section 2 Dosage and Administration:
        i. We recommend revision of the initial dosing statement to ensure all dosing information is presented in a consistent manner. The initial dose is stated in milligrams per dose (e.g. "…initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening"), whereas subsequent doses are listed in milligrams per day (e.g. "80 mg daily (40 mg morning + 40 mg evening)"). Revise the initial dosing statement to display total daily dose in a similar fashion as the 60 mg and 80 mg dosing statements (e.g. "40 mg daily (20 mg morning + 20 mg evening). A consistent display of information may help to minimize the risk of confusion and dosing errors.
        ii. Consider utilizing a table or bullet points to display the dosing information which may help to facilitate dose identification.
        iii. Consider adding the statement, "Mycapssa is given twice daily in divided doses" to this section to clarify that the total daily dose should be divided.
        iv. Include "Mycapssa capsules should be swallowed whole and should not be crushed or chewed" or a similar statement in this section. This information is listed in Section 17 Patient Counseling Information. Including this information in Section 2 of the PI may prevent incorrect manipulation of the capsule which could lead to decreased efficacy.

b. Section 16 How Supplied/Storage and Handling
    i. We request that the strength of Mycapssa capsules is added to this section in accordance with 21 CFR 201.57(c)(17)(i). We also recommend the addition of the capsule's color and imprint code to this section to facilitate product identification.
c. Instructions for Use
    i. Consider revising the statement [redacted] (b) (4) to "Take MYCAPSSA on an empty stomach." We recommend this revision due to [redacted] (b) (4) (b) (4)
    ii. Relocate Figure 2 so that is located directly below the Step "Place the tip of a thumb at the edge of a capsule's plastic cavity".
    iii. Remove the information regarding [redacted] (b) (4) (b) (4)
    iv. Consider the use of color for Figure 1 and Figure 2 to improve visibility and differentiation of the steps for opening the wallet and removing the capsule.

4.2 RECOMMENDATIONS FOR THE CHIASMA, INC

We recommend the following be implemented prior to approval of this NDA 208232:

A. Carton labeling (wallet pack)
    a. Relocate the strength statement to the upper third portion of the PDP, in close proximity to the proprietary name, to differentiate it from the net quantity statement. From post-marketing experience, the risk of numerical confusion between strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Additionally, we recommend increasing the font size of the strength statement to increase its prominence.
    b. Revise the net quantity statement [redacted] (b) (4) to read "28 capsules per wallet card" to provide clarity regarding the package type.[2]

[1] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize

c. Consider removing the statement [redacted] (b) (4) (in the Opening Instructions section) as this information already appears on the upper portion of the PDP and contributes to visual clutter. Additionally, the Opening Instructions section is focused on opening the packaging and the aforementioned statement does not address that task.
d. Increase the font size of the Opening Instructions section to increase visibility and user readability.
e. Consider revising the "Opening Instructions" section to incorporate the following recommendation:
    i. Modify Step 1 to read "Use thumb to push the button gently" to increase clarity. Revising the term [redacted] (b) (4) to read "thumb" will harmonize the Opening Instructions with the Instructions for Use.

B. Medication Card Label
a. The proprietary name, established name, and strength of the product on the principal display panel (PDP) are not prominent. Thus, we request that the font size is increased to improve user readability and identification of key information. [2]
b. Consider rotating the proprietary name, established name and strength displayed on the PDP from a vertical orientation to a horizontal orientation to be consistent with the display of other information and to improve user readability.
c. Consider including the proprietary name, established name, and strength of the product on both sides of the blue outside panel to facilitate product identification in the event that the two sides are detached.
d. Consider adding the statement "Always take with a glass of water on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal" to both of the white inside panels of the medication card. The inside of the medication card is the primary portion the users will see when removing a capsule; therefore, this appears to be a good location for this important information. Additionally, further highlighting the proper administration technique is important as taking with Mycapssa with food leads to an approximate 90% decrease in the extent of absorption.

Medication Errors. Food and Drug Administration. 2013[cited 2015 Aug 20]. Available from http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mycapssa (octreotide) that Chiasma, Inc submitted on June 15, 2015.

Table 2. Relevant Product Information for Mycapssa (octreotide)	
Initial Approval Date	N/A
Active Ingredient	Octreotide acetate
Indication	Long term maintenance treatment in acromegaly patients (b) (4) (b) (4)
Route of Administration	Oral
Dosage Form	Capsule
Strength	20 mg
Dose and Frequency	- Initial dose of 20 mg BID given orally (20 mg morning + 20 mg evening) - Dosage may be increased to 60 mg daily (40 mg morning + 20 mg evening) if IGF-1 levels increase, as determined by the physician. - If clinically necessary, may increase the dose to 80 mg daily (40 mg morning + 40 mg evening)
How Supplied	- Wallet pack with medication card containing 28 capsules
Storage	- Until first use, store unopened wallets at 36° to 46°F (2° to 8°C). Do not freeze. - After first use, opened wallets may be stored at 68° to 77°F (20° to 25°C) for up to 1 month.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 14, 2015, we searched the L:drive and AIMS using the terms, Mycapssa and octreotide, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify previous DMEPA label and labeling reviews applicable to the current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Mycapssa (octreotide) labels and labeling submitted by Chiasma, Inc on June 15, 2015.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

- Carton labeling

(b) (4)

- Container Label

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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