

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206333Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 3, 2015

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

Acting Team Leader: Jamie Wilkins Parker, Pharm.D., DRISK

Acting Deputy
Division Director: Reema Mehta, Pharm.D., M.P.H., DRISK

Subject: Review evaluates if a REMS is needed for deoxycholic acid injection

Drug Name(s): deoxycholic acid

Therapeutic Class: adipocytolytic, synthetic deoxycholic acid

Dosage form: solution for injection into pre-platysmal subcutaneous fat tissue

Application Type/Number: NDA 206-333

Applicant/sponsor: Kythera Biopharmaceuticals, Inc.

OSE RCM #: 2014-1229

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) deoxycholic acid injection. On May 13, 2014, the Agency received an original NDA from Kythera Biopharmaceuticals, Inc. (Kythera) for deoxycholic acid to improve the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults. The Applicant did not submit a proposed REMS or risk management plan for deoxycholic acid.

1.1 PRODUCT BACKGROUND

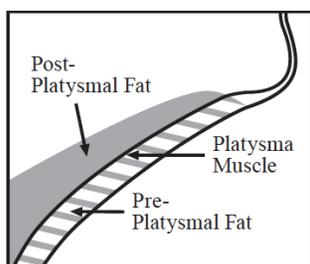
Deoxycholic acid is a synthetic version of deoxycholic acid (DCA), supplied as a solution for subcutaneous injection, to improve the appearance of subcutaneous fat in the area below the chin (i.e., SMF). As an adipocytolytic injectable drug product for submental contouring, deoxycholic acid's pharmacologic profile is first-in-class.

The proposed indication is for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults. Dosing for deoxycholic acid is as follows:

- Area-adjusted dose of 2 mg/cm² delivered at a concentration of 10 mg/mL via 0.2 mL injections spaced 1 cm apart until all sites in the planned treatment area have been injected.
- Up to 100 mg or 10 mL may be injected in a single treatment.

Up to 6 single treatments may be administered at intervals no less than 1 month apart.¹ Deoxycholic acid should only be administered into pre-platysmal subcutaneous fat tissue and NOT into post-platysmal fat (Figure 1).

Figure 1: Saggital View of Platysma Area²



Sagittal View Platysmal Area

Caution should be exercised with the use of deoxycholic acid in patients with symptoms of dysphagia, prior surgical or aesthetic treatment to the submental area, or in the presence of inflammation or induration at the proposed injection site(s).

¹ A maximum of 6 treatments were allowed during clinical trials.

² Source: Draft prescribing information for deoxycholic acid subcutaneous injection.

The Applicant intends to require prescribers to complete a “comprehensive prescriber injection training” (to include a review of anatomic structures and demonstration of correct injection technique) to further support the appropriate use of deoxycholic acid in patients with SMF. This training is consistent with the training used for investigators that participated in the clinical trials. This training will be required by the Sponsor prior to the prescriber receiving the medication for in-office administration.³

1.2 DISEASE BACKGROUND

SMF is the accumulation of fat under the chin that often presents as a “double chin.” This condition of loose or sagging skin under the chin can affect facial symmetry and attractiveness, which can lead to social embarrassment and a negative self-image in many patients. Genetics and the aging process are factors that can influence the development of SMF⁴, and diet and exercise often have minimal effects in terms of improving this condition. While liposuction procedures of the neck produce the desired effects for many patients with minimal morbidity⁵, patients with certain medical conditions or who are “psychologically unprepared” may not be appropriate candidates for these types of surgical interventions⁶.

Current treatments for improving the appearance of fullness associated with submental fat include the following:

- Cervical rhytidectomy (neck lift)- surgical procedure involving removal of localized fat deposits from the chin.
- Tumescent (neck) liposuction- liposuction involving the injection of diluted local anesthetic (e.g., lidocaine with epinephrine) into fatty areas of the neck to increase tissue firmness.

There are no injectable drug products currently approved to improve the appearance of SMF.

1.3 REGULATORY HISTORY

On May 13, 2014, the Agency received an original NDA from Kythera for deoxycholic acid to improve the appearance of moderate to severe convexity or fullness associated with SMF in adults. The Applicant did not submit a proposed REMS.

The mid-cycle meeting was convened on October 7, 2014 and the mid-cycle communication with the Applicant occurred on October 23, 2014 where the Applicant

³ ATX-101 (deoxycholic acid injection), 2.7.4 Summary of Clinical Safety, Original NDA 206333 submission for deoxycholic acid, received May 13, 2014.

⁴ Huettner F, Vasconez LO, and de la Torre JL. Neck Rejuvenation- Anatomy and Clinical Correlation. *Facial Plastic Surgery* 2012; 28(1): 40-51.

⁵ Rotunda AM, Weiss, SR and Rivkin LS. Randomized Double-Blind Clinical Trial of Subcutaneously Injected Deoxycholate Versus a Phosphatidylcholine-Deoxycholate Combination for the Reduction of Submental Fat 2009; 35(5): 792-803.

⁶ Brandt FS, Bellman B. Cosmetic Use of Botulinum A Exotoxin for the Aging Neck. *Dermatologic Surgery* 1998; 24(11): 1232-1234.

was informed that the Agency does not anticipate that the application will require a REMS.

The late cycle meeting was convened on January 27, 2015, where the Agency reiterated to the Applicant that no REMS is anticipated based on the information available at this time.

A Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) Meeting was convened on March 9, 2015 to discuss the safety and efficacy of deoxycholic acid injection for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat. While the DODAC unanimously agreed that the available safety and efficacy data support the approval of deoxycholic acid for the proposed indication, some members expressed concern with potential off-label use of the product for application sites beyond the neck area.

2 MATERIALS REVIEWED

2.1 APPLICANT'S SUBMISSIONS

The following submissions from the Applicant were reviewed for this review:

- Kythera. Original NDA 206333 submission for deoxycholic acid, received May 13, 2014 (Seq 0000)
 - Section 1.14.1 Draft Labeling
 - Section 2.5, Clinical Overview
 - Section 2.7.3, Summary of Clinical Efficacy [Indication]
 - Section 2.7.4, Summary of Clinical Safety

2.2 OTHER MATERIALS INFORMING THE REVIEW

- Kettl, D. Division of Dermatology and Dental Products. Cross-Discipline Team Leader Review for NDA 206-333, dated March 15, 2015.
- Lolic, M. Division of Dermatology and Dental Products. Clinical Review for NDA 206-333, dated March 12, 2015.
- Kovacs, S. Study Endpoints and Labeling Development (SEALD). Study Endpoint Consult Review for NDA 206-333, dated January 8, 2015.
- Khan, A. and Alexander, J. Office of Device Evaluation (CDRH Inter-center Consultative Review) for NDA 206-333, dated November 19, 2014.
- FDA. Mid-Cycle Communication to Kythera Biopharmaceuticals, Inc., dated October 23, 2014.
- FDA. Mid-Cycle Meeting (Discipline Specific Mid-Cycle Reviews) for NDA 206-333, dated October 7, 2014.

3 REVIEW FINDINGS FOR DEOXYCHOLIC ACID

The clinical development program for deoxycholic acid for the proposed indication under NDA 206-333 included 9 clinical studies [three Phase 2 studies, two Phase 3 pivotal studies, two Phase 3 supportive studies, one Phase 3B open-label treatment study and one long-term follow-up (LTFU) study]. The following pivotal Phase 3 studies formed the basis of safety and efficacy analyses:

Studies 22 and 23	
Study Design	Multi-center (US and Canada), randomized, double-blind, placebo-controlled studies
Inclusion Criteria	Adults aged 18-65 years with scores of 2 or 3 on both the clinician and patient submental fat rating scales, BMI < 40 kg/m ² and a history of stable body weight for at least 6 months
Training protocol	Study personnel responsible for administering or assisting with deoxycholic acid injections were required to complete training that included viewing an injection training video.
Treatment protocol	One to six treatment sessions scheduled 4 weeks apart. Each treatment session consisted of a maximum of 50 injections of 0.2 ML each, spaced on a 1-cm grid.
Co-Primary Endpoints	<ul style="list-style-type: none">• At least 1-grade reduction on both the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and Patient-Reported Submental Fat Rating Scale (PR-SMFRS) submental fat response scales at 12 weeks post-treatment• At least 2-grades reduction on both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment
Treatment arms and sample size	Study 22: deoxycholic acid (N=256); placebo (N=200) Study 23: deoxycholic acid (N=258); placebo (N=258)

3.1 EFFICACY

The primary efficacy endpoints were met in both pivotal studies. Deoxycholic acid was statistically and clinically more effective than placebo at 12-weeks post-treatment, with significantly more subjects receiving deoxycholic acid vs. placebo reporting at least a 1-grade reduction (improvement in amount/size of SMF) on both the CR-SMFRS and PR-SMFRS in Studies 22 and 23 respectively [(70.0% vs. 18.6%) and (66.5% vs. 22.2%)]; and at least 2-grades reduction (improvement in amount/size of SMF) in these scales in Study 22 and 23 respectively [(13.4% vs. <0.1%) and (18.6% vs. 3.0%)].

***DDDP Clinical Reviewer Comments:** Efficacy of ATX-101 [deoxycholic acid] was demonstrated in improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults when injected for up to 6 treatment sessions. It is my recommendation that one point grade improvement be accepted as valid efficacy endpoint and be included in labeling. However, it may be considered a valid endpoint only in conjunction with 2 grade improvement data for the purpose of labeling and advertising. The rationale comes from the clause in the protocol where both co-primary endpoints (starting with 2 grade improvement) were required to demonstrate statistical significance for the trial to be a success.*

There were two secondary endpoints: Magnetic Resonance Imaging (MRI) responder (a $\geq 10\%$ reduction in MRI volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in PR-SMFIS total score. Efficacy of deoxycholic acid versus placebo was also demonstrated in both trials, for both secondary endpoints ($p < 0.001$) as presented in Table 3.

Table 3: Secondary Efficacy Endpoints Analysis

Trial	Secondary Endpoints	Deoxycholic Acid	Placebo
Study 22	>10% reduction in MRI volume	(N=113) 46.3%	(N=111) 5.3%
	Change from baseline in the sum score PR-SMFIS [mean (sd)]	-3.56 (2.79)	-1.16 (2.06)
Study 23	>10% reduction in MRI volume	(N=113) 40.2%	(N=112) 5.2%
	Change from baseline in the sum score PR-SMFIS	-3.48 (2.69)	-1.42 (2.45)

DDDP Clinical Reviewer Comment: ...both secondary endpoints are supportive of primary endpoints ($p < 0.001$). The proposed language for this section of the labeling is: The proportion of ATX-101 [deoxycholic acid]-treated subjects who had at least a 10% reduction in SMF volume using MRI was greater than for the proportion of placebo-treated subjects. [REDACTED] ^{(b) (4)} and self-perceived visual attributes showed greater improvement in the ATX-101 [deoxycholic acid] group than in the placebo group.

3.2 SAFETY

The clinical program for the safety assessment consisted of 13 clinical trials in which subjects were randomized to receive deoxycholic acid (1547 subjects who received at least 1 dose) or placebo (877 subjects). Primary safety analysis was based on two adequate phase 3 placebo-controlled trials comprised of 1019 subjects (513 randomized to deoxycholic acid and 506 randomized to placebo).

The most common adverse events in the treatment arm were injection site edema/swelling (87%), injection site hematoma (72%) and injection site pain (70%). The majority of injection site reactions were reported by the Applicant as “mild to moderate” and most reactions resolved without specific treatment. Marginal mandibular nerve injuries and dysphagia occurred in 4% and 2% of deoxycholic acid-treated subjects respectively, compared to <1% for both events in placebo subjects, based on pooled data from all SMF trials.

No systemic toxicities of clinical significance were identified and no clinically meaningful changes in laboratory values or vital sign measurements considered to be “reasonably” associated with deoxycholic acid were observed. There were however, reports of hypertension (3% in deoxycholic acid subjects; 1% in placebo subjects) and “pre-syncope/syncope” (1% in deoxycholic acid subjects; 0% in placebo subjects). A

QT/QTc study was negative and according to the DDDP Clinical Reviewer⁷, these events were “most likely due to injection administration itself and/or associated pain.”

3.2.1 Primary Safety Concerns

3.2.1.1 Deaths

Five deaths were reported in the clinical development of deoxycholic acid due to the following: cholangiocarcinoma, heroin overdose, traffic accident, myocardial infarction, and pancreatic cancer; all deaths were judged to be unrelated to treatment by the study investigators and the DDDP Clinical reviewer.

3.2.1.2 Nerve Injury

At least 1 serious adverse event (SAE) was reported in 29 deoxycholic acid-treated subjects (2%) and 28 placebo-treated subjects (3%) in all SMF studies; recovered mandibular nerve injury⁸ occurred in one subject and was the only SAE considered treatment-related. According to the DDDP Clinical Reviewer, “the marginal mandibular nerve and its branches bear an important relationship with the inferior border of the mandible which is part of the treatment area.”

To mitigate the risk of mandibular nerve injury, DDDP in consult with the Center for Devices and Radiological Health (CDRH)⁹, recommends that labeling under Section 2 (Dosage And Administration) include detailed information on injection technique (including proper needle placement and administration), and highlight the importance of health care professionals administering deoxycholic acid understanding relevant submental anatomy and associated neuromuscular structures, as well as any alterations to a patient’s anatomy due to prior surgical or aesthetic procedures. Furthermore, the Applicant will require provider training prior to receiving the product for in-office use (see Section 1.1 for Product Background).

3.2.1.3 Dysphagia

Dysphagia (difficulty swallowing) was an additional primary safety concern observed during clinical development. Ten deoxycholic acid-treated subjects experienced dysphagia compared to 1 placebo-treated subject. Most episodes of dysphagia were short in duration (1-3 days) and all but one case resolved. Dysphagia will be addressed in labeling.

⁷ Lolic M. Clinical Review for NDA 206-333, dated March 12, 2015.

⁸ One subject receiving deoxycholic acid dosed at 2mg/cm² (intended marketing administration) had an event (three episodes) of mandibular nerve injury resulting in permanent discontinuation of study drug. The event eventually resolved. Important concomitant medications received by this subject during the study included botulinum toxin A for cosmetic treatment of the upper face.

⁹ Khan A and Alexander J. CDRH Inter-center Consultative Review for NDA 206-333, dated October 23, 2014.

3.2.2 Postmarketing Requirements (PMRs)/Postmarketing Commitments (PMCs)¹⁰

A Late-Cycle Meeting with the Applicant was convened on January 27, 2015 where formal discussions about PMRs and PMCs occurred. The only PMR relates to the submission of the final study report for the following ongoing trial of deoxycholic acid use in geriatric subjects aged 65-75 years of age:

- “Complete the treatment and evaluation of subjects aged 65-75 years enrolled in the ongoing ATX-101-13-28¹¹ trial. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration).”

4 DISCUSSION

The presence of SMF commonly referred to as a “double chin” not only affects a patient’s appearance, but can also negatively impact the patient socially and psychologically. While cervical rhytidectomies (“neck lifts”) and tumescent (neck) liposuction have been used to treat SMF, these procedures can be invasive; therefore not all patients (including those with certain pre-existing medical conditions) will be appropriate candidates to receive these treatments.

Deoxycholic acid is a subcutaneous injection developed to improve the appearance of moderate to severe convexity or fullness associated with SMF in adults. The benefits of deoxycholic acid were demonstrated in both pivotal studies and include statistically significant clinician and patient-reported improvement in SMF amount/size.

Based on DDDP’s assessment of the safety profile for deoxycholic acid, no systemic toxicities of clinical significance associated with the administration of deoxycholic acid were observed in the clinical development program. The most common AEs in Phase 3 studies were injection site edema/swelling (87%), injection site hematoma (72%) and injection site pain (70%); most of these events were considered “mild to moderate” and resolved without specific treatment.

Mandibular nerve injury was the only treatment-related SAE identified in Phase 3 studies. The DDDP and CDRH recommend that professional labeling for deoxycholic acid include detailed information on injection technique including proper needle placement and drug administration in the Dosage and Administration section, as there is potential for nerve injury given that the mandibular nerve and its branches bear an important anatomical relationship with the inferior border of the mandible which is part of the treatment area for deoxycholic acid. Training of investigators who administered the product was required by the Applicant during clinical trials. In addition to the professional labeling, the Applicant also intends to require prescribers to complete a comprehensive prescriber injection training to inform healthcare providers about the risks with deoxycholic acid and further ensure proper injection technique.

¹⁰ Lolic M. Clinical Review for NDA 206-333, dated March 12, 2015.

¹¹ ATX-101-13-28 is an ongoing Phase 3B study.

Other FDA approved cosmetic injection products such as onabotulinumtoxin A¹² also include detailed information on injection technique and proper needle placement in their labeling to mitigate the risk of ptosis (drooping of the eyelid) or serious events that have been reported in patients receiving onabotulinumtoxin A injections in or near vulnerable anatomic structures such as the salivary glands or the oro-lingual-pharyngeal region. Onabotulinumtoxin A does not require training prior to being shipped to a provider's office. The same provider populations (dermatologists and/or cosmetic and plastic surgeons) that are likely to prescribe and inject deoxycholic acid is the same as that of onabotulinumtoxin A and thus the Applicant for deoxycholic acid is taking mitigation measures beyond that of other products used by the same provider population which also have serious risks associated with injection technique.

Therefore, based on the currently available data, the labeling, the intended prescriber population, and the safety profile identified in the clinical trials for deoxycholic acid, DRISK believes that labeling will be sufficient to address the aforementioned risks; therefore, additional risk mitigation strategies are not warranted.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for deoxycholic acid, NDA 206-333. Deoxycholic acid has proven efficacy in improving the appearance of moderate to severe convexity or fullness associated with SMF in adults. There were no serious or severe safety issues which warrant a boxed warning for deoxycholic acid. Thus, based on the currently available data, the benefit-risk profile for deoxycholic acid is acceptable and the risks can be mitigated through professional labeling.

Should DDDP have any concerns or questions, feel that a REMS may be warranted for this product, or new safety information becomes available; please send a consult to DRISK.

¹² Onabotulinumtoxin A for injection is FDA approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients, and for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients. Detailed information on preparation and dilution technique, and administration (including proper injection technique and needle placement) is included in the product labeling in Section 2 [Dosage and Administration].

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/s/

NYEDRA W BOOKER
04/03/2015

REEMA J MEHTA
04/03/2015
I concur.