PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr BELKYRA™

deoxycholic acid injection

10 mg/mL solution

Cytolytic drug
ATC Code: D11AX

Kythera Biopharmaceuticals, Inc.
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Allergan Inc.
Markham, Ontario
L6G 0B5

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Pr BELKYRA™

deoxycholic acid injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous Injection	Solution 10 mg/mL	Benzyl alcohol. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

BELKYRA deoxycholic acid injection is indicated for:

> *Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults.*

Important Limitations of Use:

The safe and effective use of BELKYRA for use outside the submental region has not been established and is not recommended.

The safe and effective use of BELKYRA for use in patients with mild or extreme SMF has not been established and is not recommended.

Health professionals administering BELKYRA must receive specialized training before using BELKYRA and understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures.

Geriatrics (> 65 years of age):

The greater sensitivity of some older individuals cannot be ruled out; therefore caution should be exercised with these patients. The clinical trials of BELKYRA did not include sufficient numbers of subjects over age 65 to determine whether they respond differently than younger subjects.

Pediatrics (< 18 years of age):

BELKYRA is not recommended for use in children or adolescents (see Warnings and Precautions, Pediatrics).

Safety and effectiveness in patients below the age of 18 years have not been established.

CONTRAINDICATIONS

BELKYRA is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- the presence of infection in the treatment area.

WARNINGS AND PRECAUTIONS

General

BELKYRA should be administered into preplatysmal subcutaneous fat tissue and not into postplatysmal fat. BELKYRA should only be administered by a health professional who has received specialized training on the proper use of BELKYRA.

The safe and effective use of BELKYRA depends on the use of the correct number and locations for injections, proper needle placement, and administration techniques.

Health professionals administering BELKYRA must understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures.

Patients should be screened for other potential causes of submental convexity/fullness (e.g., thyromegaly and cervical lymphadenopathy) prior to use of BELKYRA.

BELKYRA should be injected mid-point into the subcutaneous fat tissue in the submental area. Injections that are too superficial (into the dermis) may result in skin ulceration and necrosis. Do not withdraw the needle from the subcutaneous fat during injection, as this could increase the risk of intradermal exposure and potential skin ulceration and necrosis. Consider withholding subsequent treatments until resolution of injection site ulceration or injection site necrosis.

Do not inject:

- into the periorbital area.
- into or within 1-1.5 cm of vulnerable anatomic structures, salivary glands, salivary duct, lymph nodes and muscles in order to avoid tissue injury.
- into or in close proximity to the marginal mandibular branch of the facial nerve to avoid the potential for motor neuropraxia, which manifests as an asymmetric smile or facial muscle weakness (see Neurologic).
- intradermally or intramuscularly.
- in patients with excessive skin laxity, prominent platysmal bands or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome.

Each vial of BELKYRA is for single patient and treatment session use only. See Dosage and Administration.

Cardiovascular

Increased Blood Pressure and Hypertension
Administration of BELKYRA may cause a temporary increase in systolic and diastolic blood pressure in healthy subjects (see Action and Clinical Pharmacology, Electrocardiography and Haemodynamics). In patients receiving treatment for submental fat, the incidence of hypertension was 2.5% with BELKYRA and 1.4% with placebo (see Adverse Reactions).

BELKYRA was not specifically studied in patients with cardiovascular disease. Use BELKYRA with caution in patients with cardiovascular disease.

BELKYRA was not specifically studied in patients with impaired circulation. BELKYRA should be used with caution in patients with impaired circulation (including diabetes mellitus).

Endocrine and Metabolism

BELKYRA was not specifically studied in patients with thyroid conditions. Thyroid disease/conditions should be ruled out prior to use as a potential contributing cause of submental convexity/fullness (i.e., thyromegaly).

Gastrointestinal

Dysphagia

Dysphagia, ranging in duration from 1-81 days (median 3 days), occurred in 2% of BELKYRA treated patients in clinical trials. BELKYRA is not recommended for patients with a history of dysphagia.

Hepatic/Biliary/Pancreatic

Patients with hepatic impairment were not specifically studied in clinical trials. BELKYRA should be used with caution in patients with hepatic impairment.

Hematologic

Injection site hematoma/bruising

In clinical trials, 72% of subjects treated with BELKYRA experienced injection site hematoma/bruising. BELKYRA should be used with caution in patients with bleeding abnormalities or who are currently being treated with antiplatelet or anticoagulant therapy as injection site hemorrhage /excessive bleeding or bruising in the treatment area may occur.

Immune

Patients taking chronic corticosteroids or patients with compromised immune systems were not specifically studied in clinical trials. BELKYRA should be used with caution in patients who are immunosuppressed (including those on chronic steroid therapy).

Neurologic

Cases of marginal mandibular nerve injury, resulting in an asymmetric smile or facial muscle weakness (paresis), were reported in 4% of BELKYRA-treated patients in clinical trials. These nerve injuries ranged in duration from 1-298 days (median 44 days). To avoid the potential for nerve injury, BELKYRA should not be injected into or in close proximity to the marginal mandibular branch of the facial nerve.

Renal

Patients with renal impairment were not specifically studied in clinical trials. BELKYRA should be used with caution in patients with renal impairment.

Skin

Superficial injection may result in skin ulceration and necrosis. BELKYRA should not be administered in the presence of inflammation or induration at the proposed injection site(s).

Caution should be used when BELKYRA is administered in patients who have had prior surgical or aesthetic treatment of the submental area. Changes in anatomy/landmarks or the presence of scar tissue may affect the ability to safely administer BELKYRA or to obtain the desired aesthetic result.

Hypopigmentation and hyperpigmentation have been observed in patients (<1%) treated with BELKYRA, especially in darker skin types.

BELKYRA should be used with caution in patients using corticosteroids.

Special Populations

Pregnant Women: BELKYRA is not recommended for use during pregnancy. No adequate and well-controlled studies in pregnant women have been performed. A study in rabbits has shown developmental toxicity (see Toxicology).

Nursing Women**:** BELKYRA is not recommended for use in nursing women.

Endogenous deoxycholic acid has been observed in human milk. Studies in nursing mothers have not been conducted.

Pediatrics (< 18 years of age): BELKYRA is not recommended for use in children or adolescents.

Safety and effectiveness in patients below the age of 18 years have not been established.

BELKYRA contains benzyl alcohol. Benzyl alcohol has been associated with respiratory distress that can be fatal when administered to preterm newborn infants of low birth weight.

Geriatrics (> 65 years of age): Use with caution in elderly patients. The clinical trials of BELKYRA did not include sufficient numbers of subjects over age 65 to determine whether they respond differently than younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of

decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see Warnings and Precautions).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse reactions (>10%) were injection site pain, localized hematoma (predominantly reported as bruising), injection site anesthesia/paresthesia, injection site edema/swelling, injection site erythema, injection site induration, injection site nodule, and injection site pruritus. Adverse reactions of nerve injury and dysphagia were also observed in BELKYRA-treated patients and lasted for several months in some cases. The proportion of patients who terminated prematurely from the pivotal trial due to adverse events was 1.6% for BELKYRA and 1.0% for placebo patients. Needle-related pain and/or anxiety can result in vasovagal responses (e.g., syncope, hypotension) or a temporary increase in blood pressure.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two Phase 3, randomized, double-blind, placebo-controlled trials 515 subjects were treated with BELKYRA and 504 subjects were treated with placebo. The study population was 19-65 years old, 85% were women, 87% Caucasian, 8% African American with a mean BMI of 29 kg/m^2, with moderate to severe submental convexity (graded as 2 or 3 on a 0 to 4 point scale) and without excessive skin laxity. Subjects received up to 6 treatments at least 1 month apart and were followed for up to 6 months after the last treatment.

Table 1: Adverse Drug Reactions Reported in ≥ 2% of BELKYRA Subjects[a]

Adverse reactions	BELKYRA (N=513) n (%)	Placebo (N=506) n (%)
Gastrointestinal Disorders		
nausea	12 (2%)	3 (1%)
dysphagia	10 (2%)	1 (<1%)
General Disorders and Administration Site Conditions		
edema/swelling	448 (87%)	218 (43%)
hematoma/bruising	368 (72%)	353 (70%)
pain	356 (70%)	160 (32%)
numbness	341 (66%)	29 (6%)
erythema	136 (27%)	91 (18%)
induration	120 (23%)	13 (3%)

paresthesia	70 (14%)	20 (4%)
nodule	68 (13%)	14 (3%)
pruritus	64 (12%)	30 (6%)
skin tightness	24 (5%)	6 (1%)
site warmth	22 (4%)	8 (2%)
nerve injury [b]	20 (4%)	1 (<1%)
Nervous System Disorders headache	41 (8%)	20 (4%)
Respiratory, thoracic, and mediastinal disorders		
oropharyngeal pain	15 (3%)	7 (1%)
Vascular Disorders hypertension	13 (3%)	7 (1%)

[a] Adverse reactions that occurred in ≥ 2% BELKYRA treated subjects and at greater incidence than placebo

[b] Marginal mandibular nerve paresis

Less Common Adverse Reactions:

General Disorders and Administration Site Conditions: Injection Site Urticaria, Administration Site Alopecia, Injection Site Ulcer, Injection Site Haemorrhage, Injection Site Discomfort

Cardiovascular: Syncope/pre-syncope

Immune: Lymphadenopathy

Nervous System Disorders: Dysgeusia

Respiratory, Thoracic and Mediastinal Disorders: Dysphonia

Skin and Subcutaneous Tissue Disorders: Pruritus, Injection Site Discolouration

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing use of BELKYRA. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

General Disorders and Administration Site Conditions:

Injection site alopecia in males, Injection site hypoaesthesia, Injection site necrosis, Hypersensitivity

DRUG INTERACTIONS

Overview

In vitro Assessment of Interactions

In vitro BELKYRA did not inhibit or induce cytochrome P450 (CYP) enzymes at clinically relevant plasma concentrations. BELKYRA does not inhibit the following transporters: P-gp, BCRP, MRP4, MRP2, OATP1B1, OATP2B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, NTCP and ASBT.

Drug-Drug Interactions

No clinical drug interaction studies have been conducted with BELKYRA.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

No studies on the effects on the ability to drive and use machines have been performed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

BELKYRA should only be used by health professionals specially trained in the use of this product.

The safe and effective use of BELKYRA depends upon the:

- selection of appropriate patients (see Warnings and Precautions),
- use of the correct number and locations of injections, and
- proper needle placement and administration techniques.

Insert the needle perpendicular to the skin for injections with BELKYRA. Patients with excessive skin laxity, prominent platysmal bands or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome should not be treated with BELKYRA.

Each vial of BELKYRA is for single patient and treatment session use only. After use, discard any remaining solution in the vial.

Recommended Dose and Dosage Adjustment

Inject 0.2 mL in each site, 1 cm apart, up to 50 injections into the subcutaneous fat. The

maximum dose should not exceed 100 mg (10 mL) in a single treatment. The number of treatment sessions needed to achieve a satisfactory response depends on the individual patient. Up to 6 treatments spaced at intervals of no less than 1 month apart are recommended based on the clinical trial efficacy and safety data. Patients should receive the minimum number of injections over a minimum number of treatment sessions to achieve a satisfactory result. More frequent dosing with BELKYRA has not been clinically evaluated for safety and effectiveness and is not recommended.

Administration

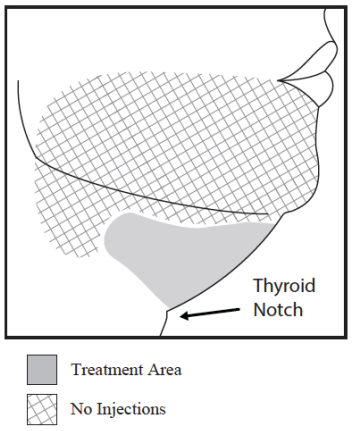
BELKYRA is supplied in ready to use, single-use vials containing 2 mL of a 10 mg/mL solution and should be clear, colourless, and free of particulate matter. Check each vial for leakage prior to administration. Visually inspect BELKYRA for particulate matter and discolouration prior to administration. Gently invert the vial several times prior to use. Do not dilute. After use, discard any remaining solution in the vial.

Injection Technique

Health professionals administering BELKYRA must receive training prior to use and understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures (see Warnings and Precautions). Needle placement is very important. To reduce the potential for motor neuropraxia of the marginal mandibular branch of the facial nerve (which may present as an asymmetrical smile):

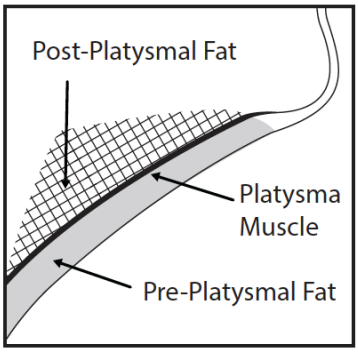
- Do not inject above the inferior border of the mandible.
- Do not inject within a region defined by a 1-1.5 cm line below the inferior border (from the angle of the mandible to the mentum).
- Inject BELKYRA only within the target submental fat treatment area (see Figures 1 and 3).

Figure 1: Avoid the Marginal Mandibular Nerve Area



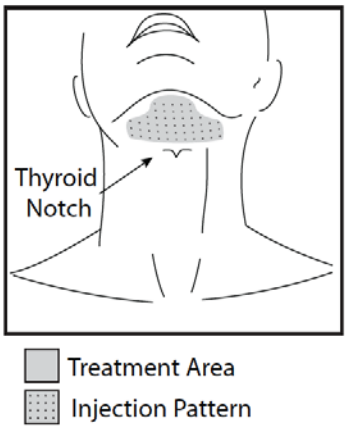
Palpate the submental area to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) at appropriate injection sites (Figure 2).

Figure 2: Sagittal View of Platysma Area



Use of ice/cold packs, topical and/or injectable local anesthesia (e.g., lidocaine) should be considered prior to administration to enhance patient comfort. The treatment area (Figure 3) should be appropriately cleansed and then outlined with a surgical pen. Apply a 1 cm^2 injection grid to mark the injection sites.

Figure 3: Treatment Area and Injection Pattern



Using a large bore needle, draw 1 mL of BELKYRA from the 2 mL vial into a sterile 1 mL syringe and expel any air bubbles in the syringe barrel. Have the patient tense the platysma. Pinch the submental fat and, using a 30 gauge (or smaller) 0.5-inch needle, inject BELKYRA next to each of the marked injection sites by advancing the needle perpendicular to the skin until it is mid-point into the underlying preplatysmal subcutaneous fat layer. Avoid injecting into the post-platysmal fat (Figure 2). Do not inject too superficially (into the dermis) or withdraw the needle while injecting as this may result in skin ulceration and necrosis. Avoid injecting into other tissues such as the muscle, salivary glands, salivary duct, thyroid gland and lymph nodes.

Inject a dose of 0.2 mL into each injection site, 1 cm apart, repeating the process using multiple vials and syringes, if necessary, until all sites in the planned treatment area have been injected. In treating patients with BELKYRA, the maximum dose should not exceed 100 mg (10 mL) in a single treatment.

Prior to each treatment session, assess the patient's submental area to ensure sufficient SMF. The number of treatment sessions needed to achieve a satisfactory response depends on the individual patient. In clinical trials, up to 6 treatments were allowed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No overdosing with BELKYRA in humans has been reported. Injection of increased volume or decreasing the spacing between injections of BELKYRA may be expected to increase risk of local adverse effects.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BELKYRA deoxycholic acid is a cytolytic drug, which when injected into tissue, physically disrupts the cell membrane.

Pharmacodynamics

Electrocardiography and Haemodynamics

A randomised, double-blind, placebo- and active-controlled, 4-arm parallel group ECG assessment study was performed to assess the effects of therapeutic (100 mg, 25 X 4 mg/cm^2 SC) and supratherapeutic (200 mg, 25 X 8 mg/cm^2 SC) single dose sessions of BELKYRA in healthy subjects with submental fat (N=54-55/treatment arm). BELKYRA was not observed to have any noteworthy effects on the QTc interval, the QRS duration, the PR interval, or ventricular heart rate over the 24 h period post-dosing.

Blood pressure assessments were performed at baseline and at 0.5 h, 2 h, and 24 h post-dosing. Following administration of the BELKYRA 100 mg and 200 mg doses, statistically significant temporary increases in systolic and diastolic blood pressure were observed at 0.5 h and 2 h post-dosing. At 2 h post-dosing, the placebo-adjusted mean change from baseline in systolic blood pressure was 4.7 mmHg (95% CI 1.3, 8.1) in the 100 mg group and 5.9 mmHg (95% CI 2.4, 9.3) in the 200 mg group and the placebo-adjusted mean change from baseline in diastolic blood pressure was 6.3 mmHg (95% CI 3.7, 8.8) in the 100 mg group and 6.0 mmHg (95% CI 3.5, 8.5) in the 200 mg group. No significant effect on systolic or diastolic blood pressure was observed at 24 h post-dosing (see Warnings and Precautions, Adverse Reactions).

Pharmacokinetics

Endogenous deoxycholic acid plasma levels are highly variable within and between individuals; most of this natural bile component is sequestered in the enterohepatic circulation loop. Pharmacokinetics of exogenous deoxycholic acid administered via treatment with BELKYRA was compared against this endogenous background.

Table 2: Pharmacokinetic Parameters (mean ± standard deviation) of BELKYRA Following a Single SC Administration to the Submental Area

Dose (mg)	C_{max} (ng/mL)	t_{max} [b] (h)	AUC_{0-24} (ng•h/mL)
Baseline (Pretreatment)	324 ± 182	12.0 (0, 24.0)	4854 ± 2339
100 [a] (N=12)	1024 ± 304	0.3 (0.1, 1.1)	7896 ± 2269

[a] BELKYRA was administered as 50 injections of 2 mg/cm^2 spaced on a 1 cm^2 grid.
[b] Presented as median (minimum, maximum).

Absorption: Deoxycholic acid from BELKYRA is rapidly absorbed following subcutaneous injection. After dosing with the maximum recommended single treatment with BELKYRA (100 mg), maximum plasma concentrations (mean C_{max}) were observed with a median t_{max} of 18 minutes after injection and mean C_{max} values were 3.2-fold higher than average C_{max} values observed during a 24-hour baseline endogenous period in the absence of BELKYRA. After maximum recommended single treatment dose (100 mg), average deoxycholic acid exposure (AUC_{0-24}) was 1.6-fold higher over endogenous exposure. Plasma AUC_{0-24} increased in a dose-proportional manner between 24 mg to 100 mg. Post-treatment deoxycholic acid plasma levels returned to the endogenous range within 24 hours and no accumulation is expected with the proposed treatment frequency.

Distribution: The volume of distribution of BELKYRA was estimated to be 193 L and is independent of the dose up to 100 mg. Deoxycholic acid is extensively bound to plasma proteins (98%).

Metabolism: Deoxycholic acid is not metabolized to any significant extent under normal conditions. In human liver microsomes, deoxycholic acid was metabolized mainly by CYP3A4 to 2 products, identified as 1β-hydroxy-deoxycholic acid and 3-dehydro-deoxycholic acid.

Excretion: Endogenous deoxycholic acid is a product of cholesterol metabolism and is excreted intact in feces (5% - 10%). Deoxycholic acid from BELKYRA joins the endogenous bile acid pool in the enterohepatic circulation and is excreted along with the endogenous deoxycholic acid.

Special Populations and Conditions

***Pediatrics*:** Clinical trials of BELKYRA did not include subjects below the age of 18 years and BELKYRA is not recommended for use in children or adolescents.

BELKYRA contains benzyl alcohol. Benzyl alcohol has been associated with respiratory distress that can be fatal when administered to preterm newborn infants of low birth weight.

Geriatrics: Clinical trials of BELKYRA did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently than younger subjects; therefore, caution should be exercised with these patients.

Baseline endogenous plasma deoxycholic acid was estimated at approximately 141 ng/mL and increased slightly with age ranging from 107 ng/mL at age 18 years to 177 ng/mL at age 64 years. Considering the high interindividual variability (51.6%), this difference was deemed of no clinical relevance.

Gender: Gender had no clinically relevant effect on the pharmacokinetics of BELKYRA based on the population pharmacokinetic analysis. Baseline adjusted AUC_{0-24} of deoxycholic acid were 23% higher in males compared to females.

Race: Deoxycholic acid pharmacokinetics was not influenced by race based on population pharmacokinetic analysis. The clinical trial population largely comprised Caucasian women (87%).

BMI: Subjects with a BMI > 30 kg/m^2 have an estimated volume that is 20% higher than subjects with a BMI ≤ 30 kg/m^2. Therefore, they are likely to have lower plasma concentrations. These differences are of little clinical consequence.

***Hepatic Insufficiency*:** BELKYRA should be used with caution in patients with hepatic impairment.

BELKYRA has not been studied in subjects with hepatic impairment. Considering the intermittent dose frequency, the small dose administered that represents approximately 3% of the total bile acid pool, and the highly variable endogenous deoxycholic acid levels, the pharmacokinetics of deoxycholic acid following BELKYRA injection is less likely to be influenced by hepatic impairment.

Renal Insufficiency: BELKYRA should be used with caution in patients with renal impairment. BELKYRA has not been studied in subjects with renal impairment. Bile acids including endogenous deoxycholic acid are excreted in the urine in negligible amounts.

Genetic Polymorphism: Deoxycholic acid is not metabolized to any significant extent; the genetic polymorphism of major Phase 1 and Phase 2 metabolic enzymes are unlikely to influence deoxycholic acid pharmacokinetics.

STORAGE AND STABILITY

Store at 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions. Each vial is for single patient and treatment session use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BELKYRA is intended only for subcutaneous injection.

BELKYRA deoxycholic acid injection 10 mg/mL solution is supplied in 2 mL, single-use vials in the following dispensing pack:

4 single-use vials

BELKYRA has a unique hologram on the vial label. If you do not see a hologram, do not use the product and call 1-844-4BELKYRA (1-844-423-5597).

Medicinal ingredients: Deoxycholic acid.

Non-medicinal ingredients: Benzyl alcohol (preservative), dibasic sodium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide, water for injection.

BELKYRA is a clear, colourless, liquid essentially free of visible particulates. The product is formulated at pH 8.3 with hydrochloric acid and has a tonicity compatible with that of biological tissues and fluids.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

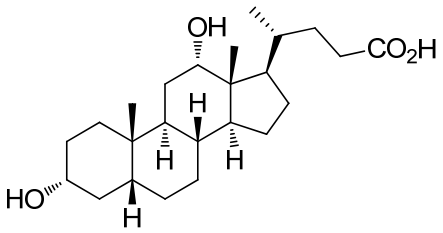
Drug Substance

Proper name: deoxycholic acid

Chemical name: 3α,12α-dihydroxy-5β-cholan-24-oic acid

Molecular formula and molecular mass: $C_{24}H_{40}O_4$, 392.57 g/mol

Structural formula:



Physicochemical properties: Deoxycholic acid is a white to off-white crystalline powder with a melting range of 172° to 175°C. Deoxycholic acid is very slightly soluble in water and it is freely soluble in basic aqueous solution.

CLINICAL TRIALS

Study demographics and trial design

Two Phase 3, randomized, double-blind, placebo-controlled trials were conducted to evaluate BELKYRA in the improvement in the appearance of convexity or fullness associated with moderate to severe SMF. The trials enrolled healthy adults (ages 19 to 65 years, BMI $\leq$ 40 kg/m^2) with moderate or severe SMF (i.e., grade 2 or 3 on 5-point validated grading scales, where 0 = none, 4 = extreme), as judged by both clinician and subject ratings. Subjects received up to six treatments with BELKYRA (N=515, combined trials) or placebo (N=504, combined trials) at no less than 1 month intervals. Use of ice/cold packs, topical and/or injectable local anesthesia was allowed during the clinical trials. Injection volume was 0.2 mL per injection site, spaced 1 cm apart into the submental fat tissue, which is expressed as dose per area as 2 mg/cm^2. For each treatment session a maximum of 100 mg (10 mL) was permitted over the entire treatment area. Subjects were administered an average of 6.4 mL at the first treatment session, and subjects who received all six treatments were administered an average of 4.4 mL at the sixth treatment session.

In these trials, the mean age was 49 years and the mean BMI was 29 kg/m^2. Most of the subjects were women (85%) and Caucasian (87%). At baseline, 51% of the subjects had a clinician-rated submental fat severity rating of moderate and 49% had a severe submental fat rating.

The co-primary efficacy assessments were based on at least 1-grade and at least 2-grade improvements in submental convexity or fullness on the composite clinician-reported (CR) and patient-reported (PR) ratings of SMF (concurrent improvement reported by both physician and patient) at 12 weeks after final treatment, relative to baseline. Additionally, as a secondary endpoint, changes in submental volume were evaluated in a subset of subjects (N=449, combined

trials) using magnetic resonance imaging.

Table 3: Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age in years	Gender
1	Phase 3, multicenter, randomized, double-blind, 2-arm, placebo-controlled	BELKYRA SC injections, 2 mg/cm^2 in up to 6 treatment sessions at ≥ 1 month intervals	506, of whom 256 received BELKYRA	49.4	43 (16.8%) Male; 213 (83.2%) Female
2	Phase 3, multicenter, randomized, double-blind, 2-arm, placebo-controlled	BELKYRA SC injections, 2 mg/cm^2 in up to 6 treatment sessions at ≥ 1 month intervals	516, of whom 258 received BELKYRA	47.9	37 (14.3%) Male; 221 (85.7%) Female

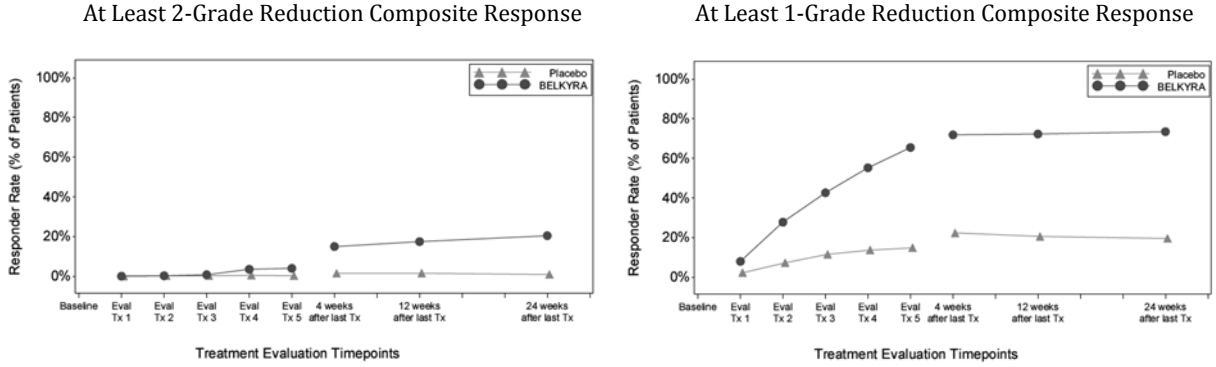
Trial results

Both 1-grade and 2-grade reductions in SMF were observed more frequently in the BELKYRA group compared to the placebo group as measured by the composite clinician and patient ratings. Approximately sixty-eight percent (68.2%) of BELKYRA-treated subjects had at least a 1-grade composite Submental Fat Rating Scale (SMFRS) response compared to 20.5% of placebo-treated subjects. Sixteen percent (16.0%) of BELKYRA-treated subjects had at least a 2-grade composite SMFRS response compared to 1.5% of placebo-treated subjects (Table 4). Subgroup analyses showed that response to treatment was reduced for non-Caucasian subjects with no difference between placebo and BELKYRA groups for 2-grade composite SMFRS in non-Caucasian subjects. The individual clinician and patient assessments of response from which the composite response is derived are provided in Figure 4. A MRI responder was prospectively defined as a subject who exhibited at least a 10% reduction in submental volume as measured by MRI from baseline to 12 weeks after last treatment. Ninety-eight (43.3%) BELKYRA-treated subjects and 12 (5.3%) placebo-treated subjects were considered MRI responders.

Table 4: Co-Primary Endpoints: > 1-Grade and > 2-Grade Composite Clinician and Patient Response 12 Weeks After Final Treatment

Endpoint	BELKYRA (N=514)	Placebo (N=508)	p-value
1-Grade Composite Response	351 (68.2%)	104 (20.5%)	<0.001
2-Grade Composite Response	82 (16%)	8 (1.5%)	<0.001

Figure 4. ≥ 2-Grade and ≥ 1-Grade Composite Clinician and Patient Response



Note: Subjects were followed up 4, 12 and 24 weeks after the last treatment. Forty-one percent of subjects received fewer than 6 treatments and entered the post-treatment period earlier than Week 24.

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

In vitro studies were conducted to determine the cytolytic effect of deoxycholic acid on different cell types including primary human epidermal keratinocytes, primary human skeletal muscle cells, primary human adipocytes, primary human fibroblasts, immortalized human melanoma cells (A375M), immortalized human cervical cancer cells (HeLa) and immortalized human thyroid cancer cells (DRO). Cells from distinct lineages displayed similar sensitivity to the cytolytic effect of deoxycholic acid, with LC_{50} (lethal concentration to 50% of cells) values ranging from 0.01% to 0.06%. Clinical concentrations of deoxycholic acid were cytotoxic to all tested cells. In vitro exposure to protein rich tissues attenuated the cytolytic effect of deoxycholic acid. Binding of deoxycholic acid to protein reduces the amount of free deoxycholic acid available for cytolysis.

In obese Zucker rats, subcutaneous injection of deoxycholic acid into the caudal lateral fat pads induced fat cell cytolysis at concentrations of ≥ 0.5%. Studies in rats also demonstrated that lipids (triolein) released from deoxycholic acid-lysed adipocytes were slowly absorbed and

processed in a manner similar to that of dietary fat. Liberated lipids were mainly distributed to the body's normal fat storage sites.

Following subcutaneous injection of 0.5% and 1% deoxycholic acid into the fat tissue of a pig, the area of cell destruction was within 1 cm of the point of injection.

Human Pharmacology

Bile acids, including deoxycholic acid and bile-acid conjugates, are secreted into the duodenum where they emulsify dietary lipids and cholesterol, facilitating their absorption. Bile acids are primarily reabsorbed (90% to 95%) and returned to the liver via the enterohepatic circulation. Efficient hepatic uptake (70% to 90%) keeps circulating bile acid levels low even after a meal. Small quantities (~ 0.3 to 0.6 g per day or 5% to 10%) of bile acids are excreted in feces; little urinary excretion occurs. Bile acid homeostasis is tightly regulated. The exogenous deoxycholic acid from BELKYRA and endogenous deoxycholic acid are indistinguishable. Therefore, the elimination and metabolism of exogenous deoxycholic acid is similar to endogenous deoxycholic acid and is regulated under the same homeostatic mechanisms. BELKYRA is intended for intermittent administration at a maximum dose of 100 mg per treatment session, which represents ~ 3% addition of exogenous deoxycholic acid relative to the endogenous bile acid pool.

High variability of 24-hour baseline deoxycholic acid levels was observed across the 167 subjects evaluated, with values ranging from below the limit of quantitation (BLOQ) (either 50 ng/mL or 25.6 ng/mL) to approximately 1700 ng/mL. Within an individual, the endogenous deoxycholic acid levels generally fluctuated across the 24-hour sampling period with no obvious time-associated trend. The average baseline measurements appear consistent over the 24-hour sampling period, ranging from 99 ng/mL at 5 hours to 212 ng/mL at 16 hours. No apparent differences in 24-hour baseline deoxycholic acid levels were observed between sexes.

TOXICOLOGY

Acute Toxicity

Single subcutaneous doses of deoxycholic acid up to 250 mg/kg in rats and up to 100 mg/kg in dogs did not cause death; however, a notable inflammatory response at, or ventral to, the site of injection was observed in both species. Subcutaneous hemorrhage, edema, focal necrosis (involving adipose tissue, muscle, or occasionally blood vessels or nerve fibers), and thrombosis were observed in rats and dogs. Ulceration and epithelial hyperplasia were also noted in rats. The severity of the local reactions limited subcutaneous administration of deoxycholic acid to 50 mg/mL (at 1 mL/kg) in rats and 20 mg/mL (at 1 mL/kg) in dogs at one injection site. The responses at the injection site diminished with time, and chronic inflammation (dog) and fibrosis (rat and dog) were observed by Day 56 post-dose.

Repeated-Dose Toxicity

Deoxycholic acid was administered by subcutaneous injection at doses of 5 to 50 mg/kg (5 to 100 mg/mL) once weekly for 4 weeks (rat and dog) or bi-weekly for up to 6 months (rat) or 9 months (dog). Doses (0.5 or 1 mL/kg) were administered to two alternating injection sites in rats, or to two alternating sets of 4 injection sites/set in dogs. The primary findings in both species were confined to the injection site and surrounding tissue, consistent with a local inflammatory

reaction at all doses tested. Transient injection site pain, minimal-to-mild erythema and edema, and localized swelling were observed which, at high doses (50 mg/kg in rats and ≥ 10 mg/kg in dogs) were associated with recoverable increases in circulating neutrophils, leukocytes and/or monocytes as a response to the local inflammation. Histologically, deoxycholic acid-related injection site lesions progressed from acute-subacute inflammation with edema, haemorrhage, and necrosis, to subacute-chronic inflammation with lesser degrees of necrosis and haemorrhage with fibroplasia and/or fibrosis, to a healing phase of mature fibrosis with minimal to no inflammatory cell infiltration by the end of the 4-week recovery period.

Across repeated-dose studies, subcutaneously administered deoxycholic acid was systemically well tolerated. No obvious signs of systemic toxicity were observed after subcutaneous injections of deoxycholic acid in rats for up to 6 months at doses of ≤ 50 mg/kg (up to 5 times the clinical dose of 100 mg, based on mg/m^2 comparison) and in dogs for up to 9 months at doses of ≤ 25 mg/kg (up to 8 times the clinical dose of 100 mg, based on mg/m^2 comparison). At the completion of dosing in the chronic 9-month dog study (20 total doses), a glomerular lipid embolus in the kidney was observed in a single male at the high dose of 50 mg/kg (16 times the clinical dose of 100 mg, based on mg/m^2 comparison).

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of BELKYRA have not been conducted.

Mutagenesis

Deoxycholic acid was negative in a battery of in vitro (microbial reverse mutation assay and chromosomal aberration test) and in vivo (micronucleus test) genotoxicity assays.

Reproductive Toxicity

Deoxycholic acid did not affect male or female fertility or early embryonic development in rats at subcutaneous doses up to 50 mg/kg (up to 5 times the clinical dose of 100 mg, based on mg/m^2 comparison) administered once weekly before cohabitation and through mating and implantation.

In embryo-fetal developmental studies, deoxycholic acid was administered subcutaneously to pregnant rats and rabbits every three days during organogenesis. No adverse effects on embryo/fetal development were observed in rats up to the highest dose tested (50 mg/kg), which corresponds to 5 times the clinical dose of 100 mg based on mg/m^2 comparison. In rabbits, missing intermediate lung lobe was observed at all doses (10, 20 and 30 mg/kg) and skeletal variations (skull irregular ossification) were observed at ≥ 20 mg/kg. These developmental effects occurred in the presence of maternal toxicity (local irritation and reduced body weight gains and feed consumption). The maternal and developmental NOAELs (no-observed-adverse-effect levels) were below 10 mg/kg (< 2 times the clinical dose of 100 mg, based on mg/m^2 comparison) in rabbits.

Deoxycholic acid at subcutaneous doses up to 50 mg/kg (5 times the clinical dose of 100 mg, based on mg/m^2 comparison) given to pregnant rats three times weekly from gestation day 7 through lactation day 20 did not harm the developing embryo or affect offspring growth and development.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

BELKYRA™

deoxycholic acid injection

Read this carefully every time your health professional administers BELKYRA. This leaflet is a summary and will not tell you everything about this drug. Talk to your health professional about your medical condition and treatment and ask if there is any new information. BELKYRA is not right for everyone. Discuss with your health professional whether BELKYRA is still right for you before each treatment.

What is BELKYRA used for?

BELKYRA is an injectable prescription medicine used in adults to improve the appearance and profile of moderate to severe amounts of fat under the chin. BELKYRA is only for use in a specific area under the chin and not for anywhere else on your body. BELKYRA is only to be administered by a health professional who has been specially trained in the use of the product.

What are the ingredients in BELKYRA?

Medicinal ingredients: Deoxycholic acid.

Non-medicinal ingredients: Benzyl alcohol (preservative), dibasic sodium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide, water for injection.

BELKYRA comes in the following dosage forms:

10 mg/mL solution for injection.

Do not use BELKYRA if you:

- are allergic to deoxycholic acid or any of the non-medicinal ingredients in the formulation.
- have an infection in your chin or neck area where the product will be injected.

To help avoid side effects and ensure proper use, talk to your health professional before BELKYRA is administered. Talk about any health conditions or problems you may have, including if you:

- have had, or plan to have, plastic surgery on your face, neck or chin, or if you have had other cosmetic treatments such as liposuction or neurotoxins (drugs sometimes used in the neck for cosmetic uses such as wrinkling or other medical reasons) in these areas.
- have, or have had, medical conditions in, on or near the neck.
- have difficulty swallowing.
- are pregnant or plan to become pregnant. It is not known if BELKYRA can harm your unborn baby.

- are breast-feeding or plan to breast-feed as BELKYRA may be found in breast milk.
- have any redness, swelling, pain or hard lumps in the area under the chin.
- have any medical condition (including high blood pressure, heart problems, coagulation (blood clotting) disorder or circulation problems, diabetes, lupus, have a compromised/weakened immune system, kidney problems, liver problems, or thyroid problems).
- have a history of skin darkening or lightening with medication.
- are taking corticosteroids used to treat joint pain and swelling.
- are younger than 18 years of age or over 65 years of age.

Tell your health professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take BELKYRA:

Your health professional will inject BELKYRA into the treatment area under your chin. Each treatment session will be scheduled at least 1 month apart until results are achieved for a maximum of 6 treatments. Your health professional will determine how many treatments you need.

Usual adult dose:

Your health professional will inject small amounts of BELKYRA in several locations in your treatment area. Your health professional will determine how many injections you need based on the amount of fat you have under your chin. You will receive multiple injections per treatment session. The total number of injections and treatment sessions needed to achieve a satisfactory response depends upon the individual.

Overdose:

If you think you have been given too much BELKYRA, contact your health professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using BELKYRA?

These are not all the possible side effects you may feel after treatment with BELKYRA. If you experience any side effects not listed here, contact your health professional. Please also see Warnings and Precautions.

You may experience pain during the injection procedure. Your pain may last for several days after treatment. In the treatment area, you may also have hair loss, bruising, swelling, numbness, redness, tingling or itchiness, and a sensation of warmth. You may experience a sensation of hardness across the treatment area or in small areas within the treatment area. Some patients reported headaches after receiving treatment.

Serious side effects and what to do about them				
	Symptom / effect	Talk to your health professional		Get immediate medical help
		Only if severe	In all cases	
Very common	Injection site bruising	✓		
Common	Nerve injury (symptoms like uneven smile after treatment)		✓	
	Trouble swallowing		✓	
	Low blood pressure immediately following treatment (symptoms like dizziness, fainting, lightheadedness)		✓	
	High blood pressure (symptoms like headache, vision problems, irregular heartbeat)		✓	
Uncommon	Open sore in the treatment area		✓	
Uncommon	Injection site problems, including open sores (ulcers), damage and tissue death (necrosis) around the injection site, allergic reaction (hypersensitivity) and excessive bleeding (injection site hemorrhage).		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your health professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to: 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

BELKYRA should be stored at 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about BELKYRA:

- Talk to your health professional
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.mybelkyra.com), or by calling 1-844-BELKYRA (1-844-423-5597).
- This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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