PACKAGE INSERT

1. PRODUCT NAME

BELKYRA™

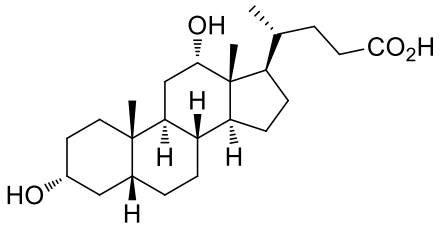
2. NAME AND STRENGTH OF ACTIVE INGREDIENT (S)

BELKYRA™ (deoxycholic acid) Injection

Each mL of the solution contains 10 mg of deoxycholic acid (10 mg/mL)

3. PRODUCT DESCRIPTION

BELKYRA™ (deoxycholic acid) injection, 10 mg/mL is a clear colorless, sterile solution for subcutaneous use. It contains a cytolytic agent, deoxycholic acid, as the active ingredient. The chemical name of deoxycholic acid is 3α,12α-dihydroxy-5β-cholan-24-oic acid, and its molecular formula is $C_{24}H_{40}O_4$, and its molecular weight is 392.57 g/mol. The chemical structure of deoxycholic acid is:



Each 2 mL vial of BELKYRA™ (deoxycholic acid) injection contains 20 mg synthetic deoxycholic acid as the active ingredient and the following inactive ingredients: benzyl alcohol (18 mg), dibasic sodium phosphate (2.84 mg), sodium chloride (8.76 mg), sodium hydroxide (2.86 mg) in water for injection, USP. Hydrochloric acid and additional sodium hydroxide are added as necessary to adjust the formulation to pH 8.3. Each vial is for single patient use.

4. PHARMACODYNAMIC/ PHARMACOKINETICS

4.1 Mechanism of Action

BELKYRA™ is a cytolytic drug, which when injected into tissue physically destroys the cell membrane causing lysis.

4.2 Pharmacodynamics

Cardiac Electrophysiology

At therapeutic doses, BELKYRA™ does not prolong the QTc interval.

4.3 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.

Absorption and Distribution

Deoxycholic acid from BELKYRA™ is rapidly absorbed following subcutaneous injection. After dosing with the maximum recommended single treatment dose with BELKYRA™ (100 mg), maximum plasma concentrations (mean C_{max}) were observed with a median T_{max} of 18 minutes after injection. The mean (±SD) C_{max} value was 1024 ± 304 ng/mL and was 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), mean (±SD) deoxycholic acid exposure (AUC_{0-24}) was 7896 ± 2269 ng.hr/mL and was 1.6-fold higher over endogenous exposure. Post-treatment deoxycholic acid plasma levels returned to the endogenous range within 24 hours. No accumulation is expected with the proposed treatment frequency.

Deoxycholic acid is extensively bound to proteins in plasma (98%).

Metabolism and Excretion

Endogenous deoxycholic acid is a product of cholesterol metabolism and is excreted intact in feces. Deoxycholic acid is not metabolized to any significant extent under normal conditions. Deoxycholic acid from BELKYRA™ joins the endogenous bile acid pool in the enterohepatic circulation and is excreted along with the endogenous deoxycholic acid.

Specific Populations

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 unlikely to be influenced by hepatic impairment.

Pharmacokinetic Effects of Gender

Deoxycholic acid pharmacokinetics were not influenced by gender.

4.4 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BELKYRA™.

BELKYRA™ was negative in a battery of in vitro (Ames test and chromosomal aberration assay in human lymphocytes) and in vivo (rat erythrocyte micronucleus assay) genetic toxicology assays.

No effects on fertility were observed in male and female rats administered deoxycholic acid at subcutaneous doses up to 50 mg/kg (5 times the MRHD based on a mg/m^2 comparison) once weekly prior to and during the mating period and through gestation day 7 in female rats.

4.5 Clinical studies

Two randomized, multi-center, double-blind, placebo-controlled trials of identical design were conducted to evaluate BELKYRA™ for use in improvement in the appearance of convexity or fullness associated with submental fat. The trials enrolled healthy adults (ages 19 to 65, BMI ≤ 40 kg/m^2) with moderate or severe convexity or fullness associated with submental fat (i.e., grade 2 or 3 on 5-point grading scales, where 0 = none and 4 = extreme), as judged by both clinician and subject ratings. Subjects received up to 6 treatments with BELKYRA™ (N=514, combined trials) or placebo (N=508, 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 also expressed in 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. Fifty-nine percent of subjects received all six treatments.

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 2-grade and at least 1-grade improvements in submental convexity or fullness on the composite of clinician-reported and patient-reported ratings of submental fat 12 weeks after final treatment. Additionally, changes in submental fat volume were evaluated in a subset of subjects (N=449, combined trials) using magnetic resonance imaging (MRI). Visual and emotional impacts of submental fat (happy, bothered, self-conscious, embarrassed, looking older or overweight) were also evaluated using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely/very much).

Reductions in submental fat volume were observed more frequently in the BELKYRA™ group compared to the placebo group as measured by the composite clinician and patient ratings (Table 1). The composite response rates by visit are presented in Figure 1.

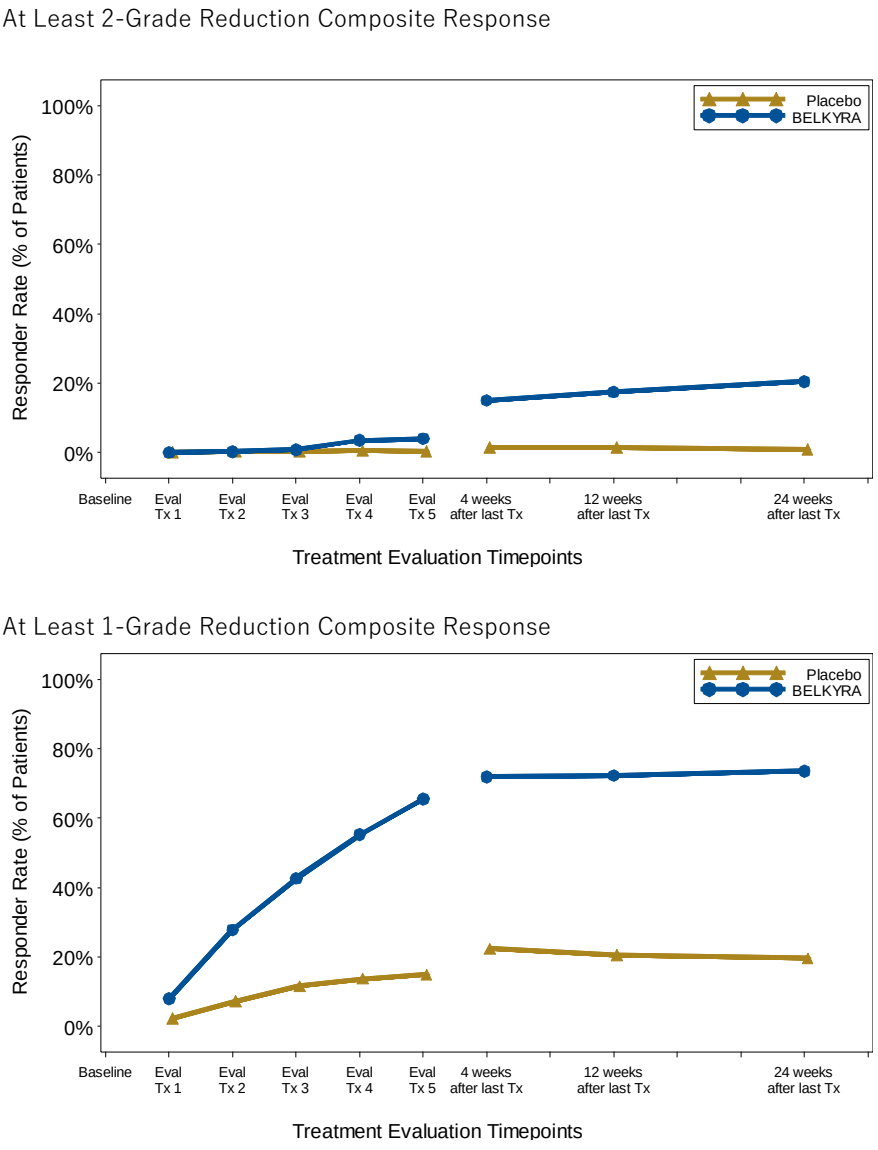
Table 1. ≥ 2-Grade and ≥ 1-Grade Composite Clinician and Patient Response 12 Weeks After Final Treatment

	Trial 1		**Trial 2**	
Endpoint	**BELKYRA™** (N=256)	**Placebo** (N=250)	**BELKYRA™** (N=258)	**Placebo** (N=258)
2-Grade Composite Response [a]	13.4%	<0.1%	18.6%	3.0%
1-Grade Composite Response [b]	70.0%	18.6%	66.5%	22.2%

[a] At least 2 grade reduction on both the clinician-reported and patient-reported ratings of submental fat

[b] At least 1 grade reduction on both the clinician-reported and patient-reported ratings of submental fat

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

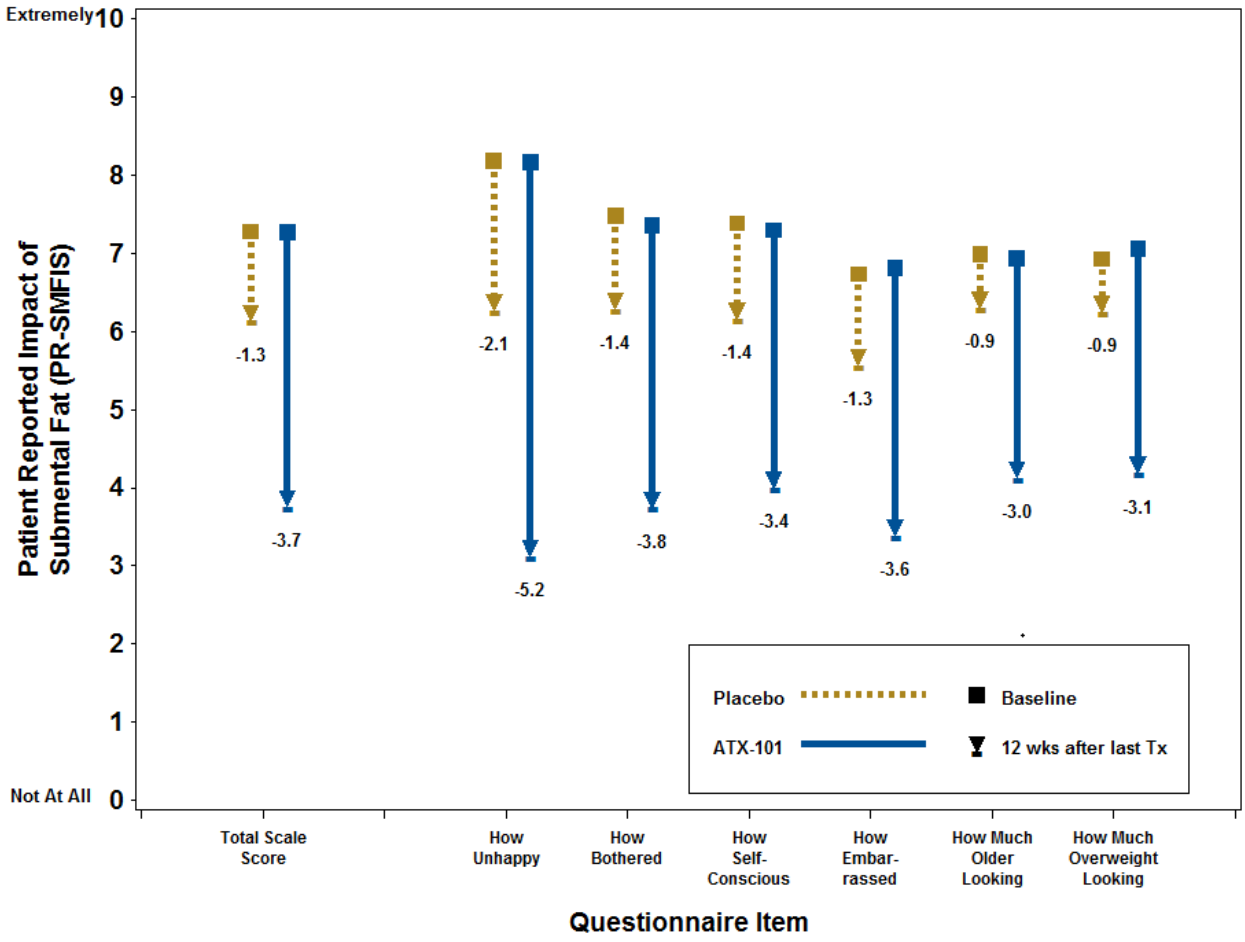


Note: Subjects were followed up 4, 12 and 24 weeks after the last treatment. Forty-one percent of subjects received fewer than 6 treatments and entered the post-treatment period earlier than Week 24.

A greater proportion of BELKYRA™-treated subjects had at least a 10% reduction in submental fat volume as compared to placebo-treated subjects when evaluated by MRI (43% vs 5%, respectively).

The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement in the BELKYRA™ group than in the placebo group, presented in Figure 2.

Figure 2. Mean SMF Impact Change 12 Weeks after Last Treatment



Despite the majority of subjects having reductions in SMF volumes, > 90.0% of subjects had no change or an improvement in skin laxity scores at Week 32 (12 weeks after last treatment) compared with baseline.

The long-term safety and maintenance of efficacy responders has been assessed following treatment with BELKYRA™. A subset of the initial BELKYRA™-treated responders continued in these follow-up studies, where maintenance of the responders has been observed for up to 5 years.

5. INDICATION

5.1 Fullness Associated with Submental Fat

BELKYRA™ (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

5.2 Limitation of use

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

6. RECOMMENDED DOSE

BELKYRA™ is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2 (0.2 mL) per injection side.

- A single treatment consists of up to maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1 cm apart.
- The maximum dose of 100 mg (10 mL or 50 injections) should not be exceeded in one treatment session
- Treatments should not be administered at intervals of less than 4 weeks
- Up to 6 single treatments may be administered in clinical trials. Most patients experience improvement following 2-4 treatment sessions

See *General Considerations for Administration (7.1) and Injection Technique (7.2)* before injection.

7. MODE OF ADMINISTRATION

Subcutaneous administration only.

7.1 General Considerations for Administration

Screen patients for other potential causes of submental convexity/ fullness (e.g., thyromegaly and cervical lymphadenopathy).

Insert the needle perpendicular to the skin for injections with BELKYRA™ .Give careful consideration to the use of BELKYRA™ 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.

Use caution 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 impact the ability to safely administer BELKYRA™ or to obtain the desired aesthetic result.

BELKYRA™ is clear, colorless and free of particulate matter. Visually inspect BELKYRA™ vials for particulate matter and/or discoloration, and discard the vial if the solution is discolored and/or contains particulate matter.

After use, discard any remaining solution in the vial.

7.2 Injection Technique

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 care 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 *[see Warnings and Precautions (9)].*

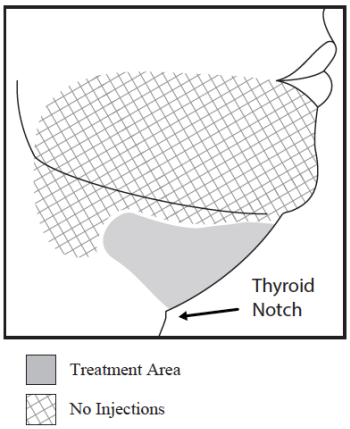
Avoid injections near the area of the marginal mandibular nerve *[see Warnings and Precautions (9.1)]*

Needle placement with respect to the mandible is very important as it reduces the potential for injury to the marginal mandibular nerve, a motor branch of the facial nerve. Injury to the nerve presents as an asymmetrical smile due to paresis of lip depressor muscles *[see Warnings and Precautions (9.1)]*.

To avoid injury to the marginal mandibular nerve:

- 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 3 and 6).

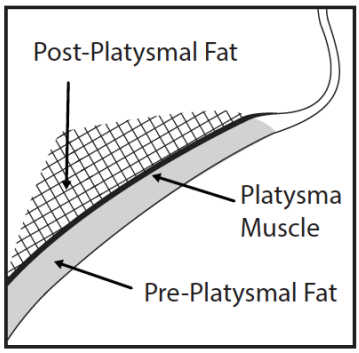
Figure 3. Avoid the Marginal Mandibular Nerve Area



Avoid injection into the platysma

Prior to each treatment session, palpate the submental area **to ensure sufficient submental fat** and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) within the target treatment area (Figure 4). The number of injections and the number of treatments should be tailored to the individual patient's submental fat distribution and treatment goals.

Figure 4. Sagittal View of Platysma Area



Injecting into the treatment area

Use of ice/cold packs, topical and/or injectable local anesthesia (e.g., lidocaine) may enhance patient comfort.

Outline the planned treatment area using anatomical landmarks with a surgical pen and apply a 1 cm^2 injection grid to mark the injection sites (Figures 5 and 6).

Figure 5. Anatomical Landmarks

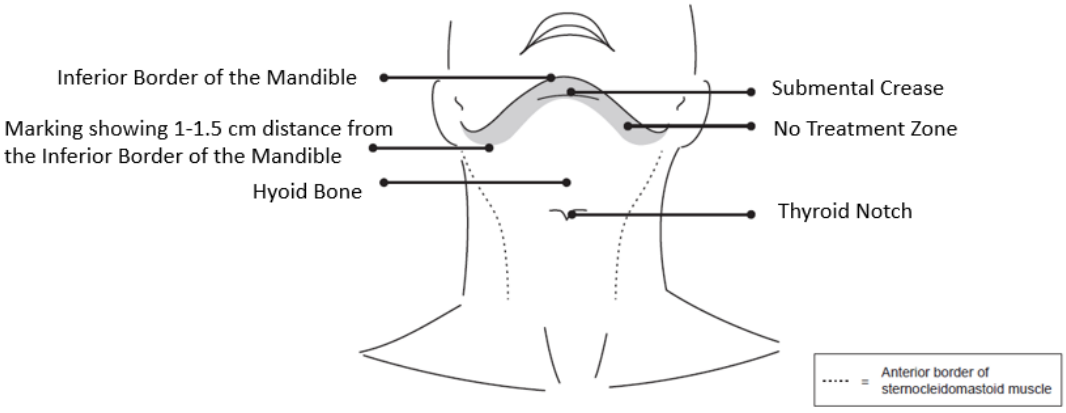
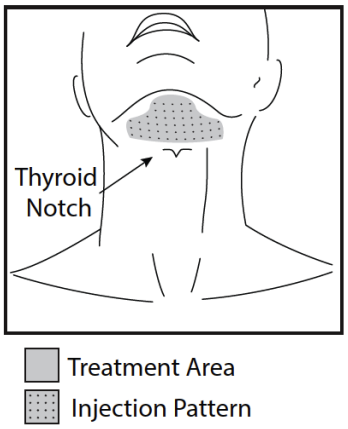


Figure 6. Treatment Area and Injection Pattern



Do not inject BELKYRA™ outside the defined parameters *[see Warnings and Precautions (9.1, 9.4)]*.

- Using a large bore needle, draw 1 mL of BELKYRA™ 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 0.2 mL of BELKYRA™ into the pre-platysmal fat (see Figure 3) next to each of the marked injection sites by advancing the needle perpendicular to the skin.
- 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.

- Avoid injecting into the post-platysmal fat by injecting BELKYRA™ into fat tissue at the depth of approximately mid-way into the subcutaneous fat layer (Figure 3).
- If at any time resistance is met as the needle is inserted, indicating the possibility of contact with fascial or nonfat tissue, the needle must be withdrawn to an appropriate depth before the injection is administered.
- Avoid injecting into salivary glands (including salivary ducts), the thyroid gland, lymph nodes and muscles; and artery or vein.
- Upon needle withdrawal, pressure may be applied to each injection site as necessary to minimize bleeding; an adhesive dressing may be applied.

8. CONTRAINDICATION

BELKYRA™ is contraindicated in the patients with the following conditions

- presence of infection at the injection sites.
- hypersensitivity to deoxycholic acid or any of the excipients

9. WARNING AND PRECAUTIONS

Injections In or Near Vulnerable Areas

Do not inject within 1-1.5 cm^2 of vulnerable anatomic structures.

Cases of marginal mandibular nerve injury, manifested as an asymmetric smile or facial muscle weakness (paresis), were reported during clinical trials. 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. All marginal mandibular nerve injuries reported from the trials resolved spontaneously.

Care should be taken to avoid inadvertent intradermal or intramuscular injection. BELKYRA™ should be injected mid-way into the preplatysmal 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. Cases

of injection site infection have been reported, some of which included cellulitis and abscess requiring additional medical treatment. Consider withholding subsequent treatments until resolution of injection site ulceration, injection site necrosis, or injection site infection.

Care should be taken to avoid inadvertent injection directly into an artery or a vein as it can result in vascular injury.

Avoid injection into salivary glands (including salivary ducts), the thyroid gland, lymph nodes and muscles. The safe and effective use of BELKYRA™ outside the SMF (submental fat) area has not been established.

Pre-existing Conditions/Treatments at or Near the Treatment Area

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

Caution should be used when BELKYRA™ is administered in patients with symptoms of dysphagia.

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 impact the ability to safely administer BELKYRA™ or to obtain the desired aesthetic result.

10. INTERACTIONS WITH OTHER MEDICAMENTS

In Vitro Assessment of Drug Interactions

No clinical drug interactions studies have been conducted with BELKYRA™. Results from in vitro studies indicate that deoxycholic acid does not inhibit or induce human cytochrome P450 (CYP) enzymes at clinically relevant concentrations. Deoxycholic acid does not inhibit the following transporters: P-gp, BCRP, MRP4, MRP2, OATP1B1, OATP2B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, NTCP, and ASBT.

11. PREGNANCY AND LACTATION

11.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BELKYRA™ in pregnant women to inform the drug-associated risk. BELKYRA™ is not recommended for use during pregnancy. In animal reproduction studies, no fetal harm was observed with the subcutaneous administration of deoxycholic acid to rats during organogenesis at doses up to 5 times the maximum recommended human dose (MRHD) of 100 mg *[see Data]*.

Data

Animal Data

Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid administered during the period of organogenesis. For the basis of comparing animal to human doses, the MRHD is 1.7 mg/kg (100 mg/60 kg). No evidence of fetal harm was observed in rats at up to the highest dose tested (50 mg/kg) which is 5-fold higher than the MRHD of BELKYRA™ based on a mg/m^2 comparison. However, missing intermediate lung lobe was noted in rabbits at all dose levels tested including the lowest dose (10 mg/kg) which is 2-fold higher than the MRHD of BELKYRA™ based on a mg/m^2 comparison. These effects may be related to maternal toxicity, which was also seen at all dose levels tested.

11.2 Lactation

Risk Summary

There is no information available on the presence of synthetic deoxycholic acid in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BELKYRA™ and any potential adverse effects on the breastfed child from BELKYRA™ or from the underlying maternal condition.

11.3 Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established and BELKYRA™ is not intended for use in children or adolescents.

11.4 Geriatric Use

The clinical trials of BELKYRA™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and

younger patients. In general, 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.

12. UNDESIRABLE EFFECTS

12.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two double-blind, placebo-controlled clinical trials 513 subjects were treated with BELKYRA™ and 506 subjects were treated with placebo. The population was 19-65 years old, 85% were women, 87% Caucasian, 8% African American. At baseline the population had a mean BMI of 29 kg/m^2, moderate to severe submental convexity (graded as 2 or 3 on a 0 to 4 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 received treatment.

The most commonly reported adverse reactions are listed below (Table 2).

Table 2. Adverse Reactions in the Pooled Trials 1 and 2[a]

Adverse reactions	BELKYRA™ (N=513) n (%)	Placebo (N=506) n (%)
Injection site reactions	492 (96%)	411 (81%)
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%)
Headache	41 (8%)	20 (4%)
Oropharyngeal pain	15 (3%)	7 (1%)
Hypertension	13 (3%)	7 (1%)
Nausea	12 (2%)	3 (1%)
Dysphagia	10 (2%)	1 (<1%)

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

[b] Marginal mandibular nerve paresis

Other adverse reactions associated with the use of BELKYRA™ include: injection site hemorrhage, injection site discomfort, injection site discoloration, pre-syncope/syncope, lymphadenopathy, injection site urticaria and neck pain.

Adverse reactions that lasted more than 30 days and occurred in more than 10% of subjects were injection site numbness (42%), injection site edema/swelling (20%), injection site pain (16%), and injection site induration (13%).

Postmarketing Experience

The following adverse reactions have been identified during postmarketing 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 aesthesia/hypoaesthesia, Injection site ulceration and Injection site necrosis, Injection site scar (secondary to skin ulceration or necrosis; and post-injection scar tissue), Injection site infection.

Immune System Disorders: Hypersensitivity

Injury, Poisoning and Procedural Complications: Vascular injury due to inadvertent intravascular injection.

Nervous System Disorders: Hypoaesthesia oral and Paraesthesia oral

13. OVERDOSE AND TREATMENT

Injection of increased volumes or decreasing the spacing between injections of BELKYRA™ may be expected to increase risk of local adverse effects.

14. STORAGE CONDITION

Store at or below 30° C.

15. DOSAGE FORMS AND PACKAGING AVAILABLE

BELKYRA™ (deoxycholic acid) injection, 10 mg/mL is a clear, colorless, sterile solution supplied in 2 mL, single patient use vials in the following dispensing pack (2 or 4 vials).
BELKYRA™ has a unique hologram on the vial label. If you do not see a hologram, do not use the product and report to your local Allergan office.

Each vial is for a single patient use. Do not dilute. Discard unused portion.

16. NAME AND ADDRESS OF MANUFACTURER

Manufactured by: Hospira, Inc. McPherson, KS 67460

17. DATE OF REVISION OF PACKAGE INSERT

Version dated: DD MMM YYYY (CCDS v8.0)