Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Belkyra 10mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 10 mg deoxycholic acid.
Each vial contains 20 mg of deoxycholic acid in 2 ml solution.

Excipient(s) with known effect

Each mL contains 4.23 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

A clear, colourless solution, free from visible particles.

The formulation is adjusted to pH 8.3 with hydrochloric acid or sodium hydroxide and has a tonicity compatible with that of biological tissues and fluids at an osmolality of 300 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Belkyra is indicated for the treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has an important psychological impact for the patient

4.2 Posology and method of administration

Posology
The total volume injected and the number of treatment sessions should be tailored to the individual patient's submental fat distribution and treatment goals.

Inject 0.2 ml (2 mg) per injection site, 1 cm apart. The maximum dose of 10 ml (100 mg equivalent to 50 injections) should not be exceeded in one treatment session.

Up to a maximum of 6 treatment sessions can be performed. Most patients experience improvement in 2 to 4 treatment sessions.

The time interval between treatment sessions should be at least 4 weeks.

To improve patient comfort during injection, oral analgesics or NSAIDs, topical and/or injectable local anaesthesia (eg, lidocaine) and/or cooling using ice gel packs may be applied to the area of injection at the discretion of the healthcare professional.

Special populations

Renal impairment
No dose adjustment is considered necessary (see section 5.2).

Hepatic impairment

No dose adjustment is considered necessary (see section 5.2).

Elderly (aged 65 years and above)
No dose adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Paediatric population
There is no relevant use of Belkyra in children or adolescents.

Method of administration
The product is indicated for subcutaneous administration only.

Belkyra should only be administered by physicians with appropriate qualifications, expertise in the treatment and knowledge of the submental anatomy. Where national guidance permits, Belkyra may be administered by appropriately qualified healthcare professionals, under the supervision of a physician. Safe and effective use of Belkyra depends on appropriate patient selection, which includes knowledge of patient history of prior interventions and their potential to alter the superficial cervical anatomy. Careful consideration should be given 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 undesirable outcome.

Belkyra must be used only for one session of injection(s) per patient and the excess of unused product must be properly disposed of.

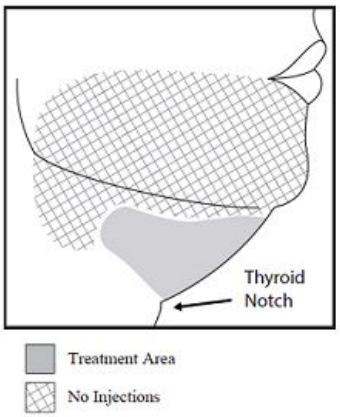
Belkyra is supplied in ready-to-use, single-use vials. Gently invert the vial several times prior to use. Do not dilute.

Insert the needle perpendicular to the skin for injections with Belkyra.

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.

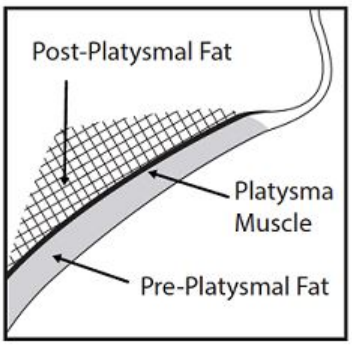
To avoid injury to the marginal mandibular nerve:
• Do not inject above the inferior border of the mandible.
• Do not inject within a region defined by a 1-1.5 cm line below the inferior border (from the angle of the mandible to the mentum).
• Inject Belkyra only within the target submental fat treatment area (see Figures 1 and 3).

Figure 1. Avoid the marginal mandibular nerve area



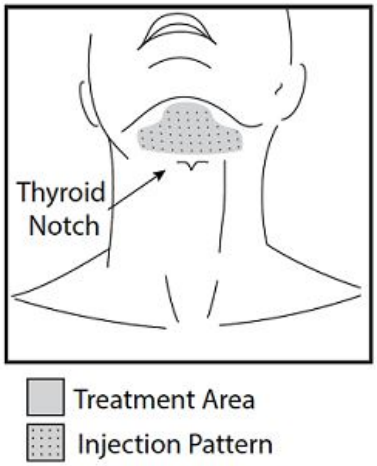
Avoid injection into the platysma. Prior to each treatment session, palpate the submental area to ensure sufficient submental fat and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) within the target treatment area (Figure 2).

Figure 2. Sagittal view of platysma area



Outline the planned treatment area with a surgical pen and apply a 1 cm^2 injection grid to mark the injection sites (Figures 2 and 3).

Figure 3. Treatment area and injection pattern



Do not inject Belkyra outside the defined parameters.

The solution for injection should be inspected visually prior to use. Only clear, colourless solutions free of visible particles should be used.

4.3 Contraindications

- Hypersensitivity to deoxycholic acid or to any of the excipients listed in section 6.1.
- Presence of infection at the proposed injection sites.

4.4 Special warnings and precautions for use

To be administered only by subcutaneous route.

Injections in or near vulnerable areas
Do not inject within 1 to 1.5 cm of vulnerable anatomic structures.

Belkyra should not be injected 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. In the clinical trials, nerve injury was temporary and all cases resolved.

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. Inappropriate injection techniques such as superficial injections, injections into blood vessels and injections without the skin marking grid, may result in skin ulceration and necrosis as well as scarring (see section 4.8). During injection the needle should not be withdrawn from the subcutaneous fat, as this could increase the risk of intradermal exposure and potential skin ulceration and necrosis. Belkyra should never be re-administered if injection site ulceration or injection site necrosis occurs. 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 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, the thyroid gland, lymph nodes and muscles.

The safe and effective use for Belkyra outside the SMF area or at higher than recommended doses has not been established.Belkyra should not be used in patients that are obese (BMI ≥ 30) or in patients who have body dysmorphic disorder.

Pre-existing Conditions/Treatments at or Near the Treatment Area
Patients should be screened for other potential causes of submental convexity/fullness (e.g., thyromegaly and cervical lymphadenopathy) prior to use of Belkyra.
Caution should be used when Belkyra is administered in the presence of inflammation or induration at the proposed injection site(s) or 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 result.

Elderly
The clinical studies of Belkyra did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients; therefore, caution should be exercised with these patients.

Excipients with known effect
This medicinal product contains 4.23 mg sodium per mL, equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been conducted with Belkyra.

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproduction studies have been performed in rats and rabbits at exposures up to 1.8 times (rat) and 12 times (rabbit) the exposure at maximum recommended human dose. While they do not indicate direct or indirect harmful effects with respect to reproductive toxicity, inconclusive findings of missing intermediate lung lobe was noted in rabbits in the embryo-fetal toxicity study (see section 5.3).

There are no adequate and well-controlled studies in pregnant women. As a precautionary measure, it is preferable to avoid the use of Belkyra during pregnancy.

Breast-feeding
There is no information available on the presence of deoxycholic acid in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because studies in nursing mothers have not been conducted, caution should be exercised when Belkyra is administered to a nursing woman.

Fertility
There are no clinical data on fertility. Belkyra did not affect general reproductive performance or fertility in male or female rats at doses up to 50 mg/kg, corresponding to approximately 5- and 3-fold exposure margins, respectively, to the maximum human recommended dose (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The data described in the underlying table reflect undesirable effects reported for Belkyra treated patients who were evaluated in the clinical studies that assessed the use of Belkyra for the treatment of submental fat.
The following side effects have been evaluated in clinical studies with the following frequencies:
- Very common (≥ 1/10)
- Common (≥ 1/100 to <1/10)
- Uncommon (≥ 1/1,000 to <1/100)

- Rare (≥ 1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse Reaction**
Nervous system disorders	Common	Headache
	Uncommon	Dysgeuisia
	Not known	Hypoaesthesia oral, paraesthesia oral
Respiratory, thoracic and mediastinal disorders	Uncommon	Dysphonia
Gastrointestinal disorders	Common	Dysphagia, nausea
Skin and subcutaneous tissue disorders	Common	Skin tightness
General disorders and administration site conditions	Very Common	Injection site: Pain, oedema, swelling, anaesthesia, nodule, haematoma, paraesthesia, induration, erythema, pruritus
	Common	Injection site: Haemorrhage, discomfort, warmth, discolouration
	Uncommon	Injection site: Alopecia, urticaria, ulcer, hypersensitivity, scar**
	Not known	Injectionsite: Hypoaesthesia, necrosis*, artery necrosis, injection site infection***
Injury, poisoning and procedural complications	Common	Injection site nerve injury
	Not known	Vascular injury due to inadvertent intravascular injection

* Adverse reactions related to injection site necrosis were reported as fat necrosis, necrosis, skin necrosis and soft tissue necrosis. These events occurred around the treatment area with affected area ranging between 0.5 cm and 3 cm. In rare cases, the entire submental area was affected.
** Injection site scarring has been reported as a result of skin ulceration or necrosis (see section 4.4) and as post-injection scar tissue.
*** Injection site infection has been reported, some of which included cellulitis and abscess (see section 4.4).

Overall, the majority of adverse reactions resolved within the treatment interval.The following table presents adverse reactions that have been reported tolast longer than the injection intervals of 4 weeks, based on results from the four phase 3 studies (N=758) in Belkyra treated patients.

Adverse Reactions	Belkyra	Mean Time to Resolution [a] (Range)
Injection site nerve injury	3.6%	53 days (1-334 days)
Injection site induration	23.4%	41 days (1-292 days)
Injection site nodule	12.0%	48 days (1-322 days)
Injection site pain	74.1%	12 days (1-333 days)
Injection site sensory symptoms	66.4%	46 days (1-349 days)
Injection site anaesthesia	61.6%	50 days (1-349 days)
Injection site paraesthesia	11.3%	27 days (1-297 days)
Injection site swelling	78.6%	15 days (1-218 days)
Dysphagia	1.5%	22 days (1-142 days)

[a]: Pertaining to Belkyra group only

In the clinical studies, some of the local reactions, such as induration, nodule, anaesthesia, pain and swelling at the injection site, and injection site motor nerve injury, were reported as not recovered within the duration of the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

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. Non-treatment area or systemic adverse reactions were infrequent during clinical studies of doses up to 200 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations
ATC code: D11AX24

Mechanism of action
Deoxycholic acid is a cytolytic drug, which when injected into localized subcutaneous fat, physically disrupts the cell membrane of adipocytes. The destruction of adipocytes elicits a tissue response in which macrophages are attracted to the area to eliminate cellular debris and lipids, which are then cleared through natural processes. This is followed by the appearance of fibroblasts and observed thickening of fibrous septa suggesting an increase in total collagen (i.e., neocollagenesis).

Clinical efficacy and safety
Four Phase 3 randomised, multi-center, double-blind, placebo-controlled trials were conducted (2 identical studies conducted in the European Union [EU] and 2 identical trials conducted in North America) to evaluate Belkyra for the treatment of convexity or fullness associated with submental fat (SMF) and the assessment of the associated psychological impact. In all trials the primary endpoints were measured 12 weeks after final treatment. Each Phase 3 trial met its primary efficacy endpoints, and showed improvement in psychological impact versus placebo.
The trials enrolled adults (ages 19 to 65) with moderate or severe convexity or fullness associated with SMF (i.e., grade 2 or 3 on 5-point grading scales, where 0 = absent, 4 = extreme), as judged by both clinician and subject ratings. Patients received up to 4 treatments in the trials conducted in the EU, and up to 6 treatments in the trials conducted in North America, with Belkyra (N=757 for all 4 studies) or placebo (N=746) at 28-day intervals. Treatment was stopped when the desired response was achieved. Injection volume was 0.2 ml per injection site, spaced 1 cm apart into the SMF 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.
The mean age in the trials conducted in the EU was 46 years and the mean BMI was 26. Most patients were women (75%) and Caucasian (94%). At baseline, 68% of the patients had a clinician-rated SMF severity rating of moderate and 32% had a severe SMF rating. For trials conducted in North America, the mean age was 49 years and the mean BMI was 29 kg/m^2. Most of the patients were women (85%) and Caucasian (87%). At baseline, 51% of the patients had a clinician-rated SMF severity rating of moderate and 49%% had a severe SMF rating.
The co-primary efficacy assessments in the EU trials were the clinician-reported ratings of SMF (CR-SMFRS) and patient assessment of satisfaction (Subject Self Rating Scale [SSRS]). Patient–reported rating of SMF (PR-SMFRS) was also assessed. Psychological impact of SMF was evaluated using multiple measures including the Derriford Appearance Scale-24 (DAS-24), the Body Image Quality of Life Inventory (BIQLI) and the Patient Reported–Submental Fat Impact Scale (PR-SMFIS) a 6-item questionnaire (assessing happiness, bothersomeness, self-consciousness, embarrassment, looking older or overweight). Statistically significant improvements in clinician- and patient-rated SMF, patient satisfaction and reduction in psychological impact of SMF were observed more frequently in the Belkyra group compared to the placebo group (Table 1). Reduction in submental fat volume was confirmed by caliper measurements.
In the studies conducted in North America, 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 (CR-SMFRS) and patient-reported (PR-SMFRS) ratings of submental fat 12 weeks after final treatment. Psychological impact of SMF was assessed using the same 6-item questionnaire as in the EU trials. In addition, changes in submental fat volume were evaluated in a subset of patients (N=449, combined trials) using magnetic resonance imaging (MRI). Reduction in submental fat volume was confirmed by both MRI and caliper measurements.
Table 1 below displays 1-Grade Clinician Response (CR-SMFRS), Patient Satisfaction Response (SSRS), and Psychological Impact (PR-SMFIS) improvement as applied to all four Phase 3 trials. Figure 4 provides the response rates based on clinician SMF ratings at each study visit.

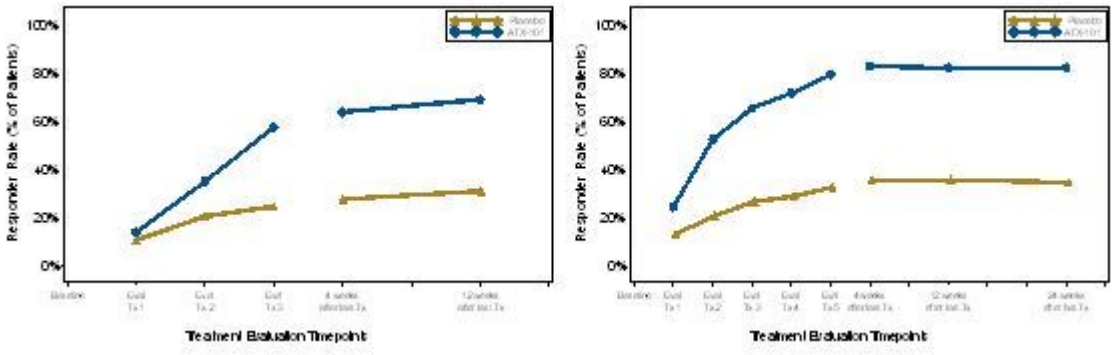
Table1: Clinician and Patient Ratings of SMF, Satisfaction and Psychological Impact 12 Weeks After Last Treatment

	Trials conducted		**Trials conducted**	

	in the EU [a]		in North America [b]	
Endpoint	**Belkyra** (N=243)	**Placebo** (N=238)	**Belkyra** (N=514)	**Placebo** (N=508)
1-Grade Clinician Response (CR-SMFRS) [c]	63.8%	28.6%	78.5%	35.3%
1-Grade Patient Response (PR-SMFRS) [c]	63.1%	34.3%	80.3%	38.1%
Patient Satisfaction Response (SSRS) [d]	65.4%	29%	69.1%	30.5%
Psychological Impact (PR-SMFIS) Percent Mean Improvement from Baseline [e]	44.6%	18.0%	48.6%	17.3%

[a] Up to 4 treatment sessions permitted
[b] Up to 6 treatment sessions permitted
[c] At least a 1-grade reduction in the clinician-reported ratings (CR-SMFRS) of SMF 12 weeks after last treatment
[d] A patient rating of "extremely satisfied", "satisfied" or "slightly satisfied" on the SSRS 12 weeks after last treatment
[e] Percent mean improvement from baseline calculated as the PR-SMFIS mean change from baseline divided by the baseline mean

Figure 4: Clinician SMF Rating (CR-SMFRS) 1-Grade Responder Rates at Each Study Visit; Pooled Data From EU Trials (Left Panel) and North America Trials (Right Panel)*



* $p < 0.001$ for all time points, Belkyra vs. Placebo
Despite the majority of patients having reductions in SMF volumes, 90.0% and 92% of patients in the EU and US/Canada trials respectively, had no change (68.9% and 70.5%) or an improvement (21.6% and 22.9%) in skin laxity scores 12 weeks after last treatment compared with baseline.
The long-term safety and maintenance of treatment effect has been assessed following treatment with Belkyra. A subset of the initial Belkyra-treated responders continued in these follow-up studies, where maintenance of treatment effect has been demonstrated for up to 5 years.

Paediatric population
The use of Belkyra is not recommended in individuals under 18 years.

The European Medicines Agency has waived the obligation to submit the results of studies with Belkyra in all subsets of the paediatric population in treatment of moderate to severe convexity or fullness associated with submental fat in adults when the presence of submental fat has a psychological impact for the patient (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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 6 minutes after injection. The mean C_{max} value was 1 036 ng/ml and was 2.3-fold higher than average C_{max} values observed during a 24-hour baseline endogenous period in the absence of Belkyra. At the maximum recommended single treatment dose (100 mg), deoxycholic acid exposure (AUC_{0-24}) was less than 2-fold higher over endogenous exposure. Plasma AUC_{0-24} increased in a dose-proportional manner up to 100 mg. Post-treatment deoxycholic acid plasma levels returned to the endogenous range within 24 hours. No accumulation is expected with the proposed treatment frequency.

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

Elimination
Endogenous deoxycholic acid is a product of cholesterol metabolism and is excreted intact in feces. Deoxycholic acid from Belkyra joins the endogenous bile acid pool and is excreted along with the endogenous deoxycholic acid.Deoxycholic acid is eliminated via hepatic transport proteins from the blood to the bile without any significant contribution of metabolism.
Deoxycholic acid is not an in vitro inhibitor of the enzymes CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. Deoxycholic acid did not induce CYP1A, 2B6 and 3A at a clinically level.
Deoxycholic acid is not an in vitro inhibitor of the transporters BSEP, MRP2, MRP4, MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, OATP2B1 and ASBT. Deoxycholic acid inhibited NTCP with an IC50 of 2.14 µM in vitro.

Renal impairment
Belkyra has not been studied in patients with renal impairment. Bile acids including deoxycholic acid are excreted in the urine in negligible amounts; renal impairment is unlikely to influence deoxycholic acid pharmacokinetics.

Hepatic impairment
Belkyra has not been studied in patients 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.

Elderly
No dose adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.
Carcinogenicity
In repeat dose toxicity studies of up to 6 months in rats and 9 months duration in dogs, there was no indication of local or systemic pre-neoplastic responses to subcutaneous Belkyra administration. In these studies, the maximum intended clinical dose was exceeded by 2.5 to 12.5-fold (based on mg/injection site) and 2 to 3-fold (based on quantified systemic exposure) in rats and dogs, respectively. Further, in contrast to the maximum intended clinical regimen of monthly injections for up to 6 sessions, Belkyra injections were administered twice monthly for up to 13 total doses in rats and 20 total doses in dogs. No carcinogenicity studies have been conducted with Belkyra.
Genotoxicity
Belkyra was negative in a standard battery of in vitro (microbial reverse mutation assay and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicology assays.
Developmental toxicity
Inconclusive findings of missing intermediate lung lobe were noted in rabbits in the embryo-fetal toxicity study. The finding was significantly increased in the 30mg/kg group but was evident also at the lowest concentration 10mg/kg. This dose was associated with maternal local toxicity. The clinical significance of the finding is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection
Sodium chloride
Sodium hydroxide (for dissolution and pH adjustment)
Disodium phosphate anhydrous
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months
The product should be used immediately once the vial stopper has been penetrated.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Solution for injection in a vial (Type I glass), fitted with a stopper (chlorobutyl rubber) and a seal (aluminium) with flip-top lid (polypropylene).

One carton contains 4 vials. Each vial contains 2 ml solution for injection.

6.6 Special precautions for disposal and other handling

Each vial is for single patient use only. After use, discard any unused product.

Belkyra shall be prepared for injections in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap is damaged, do not use.
2. Attach a large bore sterile needle to a sterile single-use 1 ml syringe.
3. Introduce the large bore sterile needle into the stopper of the vial and draw 1 ml of Belkyra into the 1 ml syringe.
4. Replace the large bore needle with a 30 gauge (or smaller) 0.5-inch needle. Expel any air bubbles in the syringe barrel before injecting the product into the subcutaneous fat.
5. To withdraw remaining contents of the vial, repeat steps 3 and 4.

7 MARKETING AUTHORISATION HOLDER

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1824/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd June 2017
Date of latest renewal: 29th June 2021

10 DATE OF REVISION OF THE TEXT

May 2023