Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Deoxycholic acid

Proprietary Product Name: Belkyra

Sponsor: Allergan Australia Pty Ltd

April 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR	Adverse Drug Reaction
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
ASBT	Apical sodium bile acid transporter
ASCOM	Advisory Committee on the Safety of Medicines
AUC	Area under the plasma drug concentration-time curve
$AUC_{0\text{-last}}$	Area under the plasma drug concentration-time curve up to last measurable drug concentration
BA	Benzyl alcohol (preservative)
BMI	Body mass index
BSEP	Bile salt export pump
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum drug concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Clinician reported
CR-SMFRS	Clinician Reported Submental Fat Rating Scale
CYP	Cytochrome p450
DAE	Discontinuation due to adverse event
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union

Abbreviation	Meaning
FDA	Food and Drug Administration (United States)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Health care professional
hERG	Human ether-à-Go-Go gene
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
ka	First order absorption
LS mean	Least squares mean
MAH	Marketing Authorisation Holder
MRI	Magnetic resonance imaging
NMT	Not more than
NTCP	Sodium taurocholate co-transporting polypeptide
PI	Product Information
PR-SMFRS	Patient Reported Submental Fat Rating Scale
QTc	Corrected QT-interval
RACS	Royal Australasian College of Surgeons
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SMFRS	Submental Fat Rating Scale
SSRS	Subject Self Rating Scale
TEAE	Treatment emergent adverse events

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum serum drug concentration
US	United States (of America)
V_d	Volume of distribution
w/v	Weight/volume

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	19 July 2016
Date of entry onto ARTG	21 July 2016
Active ingredient(s):	Deoxycholic acid
Product name(s):	Belkyra
Sponsor's name and address:	Allergan Australia Pty Ltd Locked Bag 1514, Pymble, New South Wales 2073
Dose form(s):	Solution for injection
Strength(s):	10 mg/1 mL
Container(s):	Vial
Pack size(s):	4 x 2 mL vials
Approved therapeutic use:	*Belkyra (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.*
Route(s) of administration:	Subcutaneous (SC)
Dosage:	*Belkyra is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2.* *A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1 cm apart.* *Up to 6 single treatments may be administered at intervals no less than 1 month apart.*
ARTG number (s):	233201

Product background

This AusPAR describes the application by Allergan Australia Pty Ltd to register deoxycholic acid for injection (proprietary name: Belkyra) as a new chemical entity.

The proposed indication is:

> *for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.*

This submission proposes the registration of a single dosage and dose form of the drug product. The undiluted product is injected into subcutaneous (SC) fat tissue in the

submental area using an area adjusted dose of 2 mg/cm^2. A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), and spaced 1 cm apart. The maximum (daily) dose is 100 mg of deoxycholic acid (or total of 10 mL or 50 x 0.2 mL injections of the product). Up to 6 single treatments may be administered at intervals no less than 1 month apart.

Deoxycholic acid itself is a small, fully synthetised new active ingredient that is structurally identical to endogenous deoxycholic acid. The product itself is 1% deoxycholic acid and there are no novel excipients in the product. Once injected into submental fat, it results in a reduction of fat by cytolysis of fat cells.

Belkyra (deoxycholic acid) has been developed as a '*potential first-in-class, adipocytolic, submental-contouring, injectable drug*' for the treatment of undesired submental fat. Belkyra is a cosmetic treatment for submental fat that presents as '*an unappealing submental profile, convexity or fullness that negatively affects the satisfaction and well-being of a substantial proportion of the population'*. Submental fat is a common condition and is not related to any co-morbidity. It is more common with aging and occurs in both men and women. Not all subjects with submental fat are bothered by the condition, as the sponsor reports that '*34% of those with marked submental fat reported being bothered by their submental fat*' hence, the morbidity associated with the condition is psychosocial.

Currently available treatments for this condition are limited and include surgical procedures performed under general anaesthetic and targeted liposuction. These currently available treatments can be associated with significant morbidity and may have a suboptimal outcome.

Belkyra was originally submitted to the TGA for evaluation under the proprietary drug product name 'Kybella' by Kythera Pharmaceuticals Australia Pty Ltd. After Round 2 of the clinical evaluation, the proprietary product name was changed from Kybella to Belkyra and transferred from Kythera Pharmaceuticals Australia Pty Ltd to Allergan Australia Pty Ltd. These changes are discussed in the summary of Delegate's overview found under the section '*Overall conclusion and risk/benefit assessment of this document*' towards the end of this AusPAR. For clarity and continuity, where the drug product is mentioned by tradename, Belkyra has been used throughout this document.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 21 July 2016 (this application).

At the time the TGA considered this application, similar applications were approved or under consideration in other jurisdictions as summarised in Table 1 below.

Table 1: International regulatory status

Jurisdiction	Submission date	Approval date	Indications
Canada	August 2014	April 2015	For the '*improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults'*
US	August 2014	July 2015	As above

Jurisdiction	Submission date	Approval date	Indications
Switzerland	October 2014	Under evaluation	As above
EU[1]	30 June 2016	Positive opinion	As above with the addition of '*when the presence of submental fat has a psychological impact for the patient*'

(1) Via the Decentralised Procedure with Sweden acting as Reference Member State

Product information

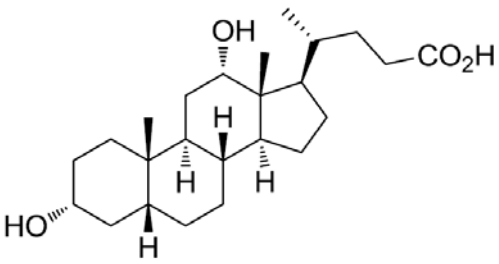
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Deoxycholic acid (structure shown in Figure 1 below) is an endogenous bile acid that solubilises dietary lipids in the digestive tract of humans and other animals thereby aiding in digestion and absorption of fats. The deoxycholic acid drug substance used in the product is synthetically derived.

Figure 1: Deoxycholic acid drug structure



Drug substance (active ingredient)

Deoxycholic acid has 10 stereogenic centres and is dextrorotatory. The stereochemistry of the drug substance is controlled by acceptable specific optical rotation specification limit +52.0° to +58.0°. There are several known polymorphic forms of the drug substance, with one predominant form (Form B). The commercial manufacturing process yields Form B, which is ensured by Fourier transform infrared spectroscopy identification in the drug substance specification; however, given that deoxycholic acid is completely dissolved in the finished product, control of polymorphic form (as well as particle size distribution) is not considered critical.

The specification limit of ≤ 0.15% for three specified impurities are in line with the International Conference on Harmonisation (ICH) qualification threshold for the

maximum (daily) dose of 100 mg. Single unspecified impurities are controlled at ≤ 0.10% which complies with the ICH identification threshold.

The specification limits for the residual solvents used in the synthesis (dichloromethane, ethanol, methanol, n-heptane and tetrahydrofuran) all comply with the ICH guideline. The specification limit for one residual (which is not included in the ICH guideline)was acceptable to the chemistry evaluator.

The manufacturing and quality control of the drug substance (including the drug substance specification) are acceptable.

Drug product

The proposed drug product is an isotonic injectable solution that contains 10 mg/mL of the active ingredient, deoxycholic acid and five conventional excipients including sodium hydroxide, dibasic sodium phosphate, sodium chloride and hydrochloric acid. The product does not contain any antimicrobial preservative. The excipients used are commercially sourced and are controlled to compendial standards.

The quality of the product is controlled by acceptable specification that includes tests and limits for appearance, identification, colour, clarity, pH, fill volume, osmolality, assay, related substances, particulate matter, sterility and bacterial endotoxins.

There are no specified degradation products. The unspecified degradation products are limited to not more than (NMT) 0.20% at release and expiry which is in line with the ICH Q3B(R2) identification threshold of 0.2% for the maximum daily dose of 100 mg.[1] This is acceptable.

The analytical methods used to analyse the product were adequately described and validated.

Acceptable Good Manufacturing Practice (GMP) clearance was provided for the drug substance manufacturer but the GMP clearance for the finished product manufacturer will expire on 24 April 2016 which is prior to the decision date 15 July 2016. This issue has been raised in the clinical evaluation report.

The stability data supplied supported a shelf life of 24 months for the unopened product when it is stored below 30 °C.

Biopharmaceutics

The sponsor has not performed any absolute bioavailability study in humans. The sponsor has provided justification for not performing an absolute bioavailability study on the basis that the proposed product is a simple SC solution for injection intended to be locally acting. This justification was acceptable from a pharmaceutical chemistry perspective.

Advisory committee considerations

The application has not been considered by the Pharmaceutical Sub-Committee of the ACPM because no issues requiring their expertise were identified during the chemistry and quality evaluation.

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use : ICH Harmonised Tripartite Guideline - Impurities In New Drug Products Q3b(R2); Current *Step 4* Version dated 2 June 2006.

Quality summary and conclusions

If the presentation is acceptable from a clinical perspective, then there was one outstanding issue relating to the GMP clearance for the finished product manufacturer. This issue was raised in the clinical evaluation report. All other issues raised with the chemistry and quality aspects of the submission have been adequately resolved and these aspects are now acceptable. When the outstanding GMP issue has been satisfactorily resolved, then approval can be recommended with respect to chemistry and quality control.

Updated GMP clearance was obtained on 5 April 2016 for the finished product manufacturer. This is valid until 24 October 2016 and approval is now recommended with respect to chemistry and quality control.

III. Nonclinical findings

Introduction

The nonclinical dossier was a hybrid literature-based submission, containing mostly original studies together with published literature reports that dealt mainly with pharmacokinetics. The quality of the nonclinical dossier was satisfactory. All critical safety-related studies were Good Laboratory Practice (GLP) compliant.

The sponsor initially proposed a preserved formulation for registration containing 0.9% benzyl alcohol (BA). A preservative-free formulation was subsequently proposed at Round 2 in response to the TGA Microbiology Evaluation Report issued at Round 1. Most of the nonclinical studies were conducted with deoxycholic acid in vehicle containing 0.9% BA. To support the revised formulation, potential differences in the toxicity profile due to the removal of the BA component were investigated in a 4 week repeat-dose toxicity study in rats where deoxycholic acid formulations with and without 0.9% BA were directly compared.

Pharmacology

Primary pharmacology

Deoxycholic acid is a secondary bile acid, ordinarily produced in the liver and gastrointestinal tract, which aids in the solubilisation and absorption of fats from food passing through the digestive tract. The surfactant properties of deoxycholic acid are the pharmacological basis for its proposed mechanism of action, whereby high local concentrations of deoxycholic acid after SC injection are expected to disrupt lipid bilayers of cell membranes causing cytolysis and cell death of adipocytes.

The sponsor provided a number of studies that demonstrated cytolysis of deoxycholic acid under in vitro and in vivo conditions. Studies were also conducted to investigate whether the compound had cell specific actions and conditions affecting its cytolytic activity.

Through in vitro experiments with cultured cells, all cell types tested (specifically human keratinocytes, adipocytes, fibroblasts, skeletal muscle myocytes, and various cancer cell lines) were found to be sensitive to lysis by deoxycholic acid, with only modest differences in potency seen. Cytotoxicity was evident at concentrations of deoxycholic acid 0.01% weight/volume (w/v) and higher, with loss of nuclear staining, hyaline necrosis and loss of cell membrane integrity being indicators of cytolysis. The cytolytic effects were found to be attenuated by the presence of collagen and bovine serum albumin in the culture

medium, consistent with binding of deoxycholic acid to hydrophobic surfaces of the proteins acting to reduce the amount of free drug available for cytolysis. As well, co-incubation with muscle and skin tissue (and less so fatty tissue) was shown to attenuate the drug's lysis of A375M cells (human melanoma cell line), attributed to the protein content of these tissues (highest for muscle and skin; lowest for fat).

In vivo, injection of deoxycholic acid (0.1%, 0.25%, 0.5% and 1%) into fat pads in obese rats produced dose-dependent adipose necrosis (assessed 24 h post-dose). Effects at strengths 0.25% and lower were comparable to vehicle (0.9% BA). In a pig, histological examination of the areas surrounding sites of SC injection revealed inflammation (minimal at 0.5% strength; mild to moderate at 1%) and apoptotic adipocytes most prominent within 0.5 cm or 1 cm of injection and virtually absent at distances > 1 cm.

Secondary pharmacodynamics and safety pharmacology

No receptor screen with deoxycholic acid was submitted. A study with its synthetic precursor (DCA-129), with which it shares some structural similarity, was performed against a limited panel of steroid receptors and showed the compound to have no or only weak affinity for human glucocorticoid, oestrogen, androgen and progesterone receptors.

A series of studies examining the pharmacokinetics of radiolabelled lipid (14C-tiolein) following SC administration to deoxycholic acid-treated sites showed slow systemic distribution of released lipid, with metabolism and excretion seen to occur by known lipid pathways.

Safety pharmacology studies covered the core battery of systems (central nervous system (CNS), cardiovascular and respiratory systems). IV (intravenous) administration of deoxycholic acid at 10 mg/kg caused immediate transient central nervous system (CNS) effects in rats (decreased motor activity, whole body tremors, loss of righting reflex, hyperpnoea, coldness to touch, ptosis and lacrimation); no CNS effects were evident at 5 mg/kg IV. Cardiovascular and respiratory effects in dogs were limited to a mild and transient increase in heart rate at the highest dose level tested (20 mg/kg SC); electrocardiogram (ECG) waveforms were otherwise unaffected. In vitro, deoxycholic acid caused a gradual and irreversible loss of a potassium current (IKr) in human Ether-à-go-go-related gene (hERG) expressing Chinese hamster ovary (CHO) cells (at concentrations ≥ 1 μM) but this most likely reflects loss of cell membrane integrity rather than actual channel blockade.

Pharmacokinetics

Absorption of subcutaneously administered deoxycholic acid was generally rapid (the time of peak plasma concentration (T_{max}) typically ≤ 1 h) in all laboratory animal species examined (rats, rabbits and dogs) as in humans. Bioavailability by the SC route was essentially 100% in rats and dogs. Due to extensive enterohepatic recycling of both endogenous and exogenously administered deoxycholic acid, elimination half-lives and clearance values could not be readily ascertained.

Deoxycholic acid readily binds to serum albumin with 98% plasma protein binding reported for human subjects. Analogous plasma protein binding data for animals were not presented. Tissue distribution of radioactivity in rats after SC administration of radiolabelled (3H) deoxycholic acid was rapid and wide, with the small intestine and liver the systemic tissues showing the highest levels of radioactivity. Distribution to the brain was negligible. Low levels of radioactivity were still detected in the intestinal contents 7 days post-dose (reflecting known enterohepatic recycling of deoxycholic acid and slow elimination).

The metabolic fate of SC administered exogenous deoxycholic acid was not characterised in dedicated animal studies as the process of biosynthesis and recycling of bile acids is well known and integration into the endogenous pool of bile acids can be expected. Briefly, free bile acids in the liver form taurine or glycine conjugates and are secreted into the small intestine to participate in digestive processes. These are then actively reabsorbed by the ileum or continue into the caecum where they are subject to bacterial deconjugation and in the case for primary bile acids, 7-dehydroxylation. Passive diffusion of bio-transformed bile acids enables them to be returned into the endogenous pool of bile acids in the liver.

Similarly, dedicated mass balance studies on exogenous deoxycholic acid were not performed in nonclinical species as excretion of bile acids is well reported in the literature. The primary excretory route in healthy mammals is through faeces. The amount of deoxycholic acid excreted varies across species with deoxycholic acid accounting for 39.5%, 36% and approximately 4% of the total bile acids excreted in rats, rabbits and humans, respectively (equating to approximately 4.6 mg, 0.22 mg and 0.34 mg deoxycholic acid per gram of faeces). Under healthy conditions, urinary excretion is negligible.

Pharmacokinetic profiles in animals and humans display sufficient similarity to allow the nonclinical species to serve as appropriate models for assessing the toxicity of deoxycholic acid.

The plasma kinetics of deoxycholic acid (SC administration) was not affected by the removal of 0.9% BA from the formulation in rats. In humans, a higher mean area under the plasma drug concentration-time curve (AUC) was observed with administration of the preservative-free formulation compared with 0.9% BA (20% based on geometric means and 32% based on arithmetic means), while maximum concentration of drug in serum (C_{max}) values were equivalent. Considering the variability of exposure and the confounding influence of endogenous deoxycholic acid, there appears to be no obvious difference in clinical pharmacokinetics between preserved and unpreserved formulations.

Pharmacokinetic drug interactions

Deoxycholic acid (≤ 100 μM) exhibited negligible inhibitory activity against cytochrome P450 enzymes (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 in experiments with human liver microsomes, and caused no significant induction of CYP 1A, 2B6 or 3A in experiments with cultured human hepatocytes.

Deoxycholic acid is a substrate for a number of uptake transporters including the apical sodium bile acid transporter (ASBT), bile salt export pump (BSEP) and sodium taurocholate co-transporting polypeptide (NTCP) and relies on these interactions for enterohepatic recycling. Deoxycholic acid exhibited inhibitory activity against all tested efflux and uptake transporters (BSEP, MRP2, MRP4, P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, NTCP and ASBT). Half maximal inhibitory concentration (IC_{50}) values though were extreme multiples (≥ 360 times) of the clinical C_{max} for unbound drug at the maximum recommended human dose for all transporters except the hepatic uptake transporter NTCP where the IC_{50} (2.14 μM) was 43 times higher than the clinical peak free concentration (0.05 μM). Overall, based on these data and given the pattern of use, no clinically significant pharmacokinetic drug interactions are considered likely to be encountered in patients.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in rats and dogs using the clinical (SC) and IV routes. No mortality or clinical signs indicative of overt systemic toxicity were seen up to the highest doses tested (250 mg/kg SC and 10 mg/kg IV in rats; 100 mg/kg SC and 5 mg/kg IV in dogs; up to between 23 to 30 times the maximum recommended clinical dose on a body surface area basis) although the post-dose observation period was frequently only short (commonly a day or week after dosing). In studies with extended observation periods (≥ 14 days post-dose), maximum non-lethal doses of 10 mg/kg SC were established in both species. Injection site changes included discolouration or reddening, scabbing, thickening, gelatinous material, focal necrosis, ulceration, acute or chronic inflammation and skeletal muscle degeneration. These were the chief findings in all studies. Suppression of body weight gain or body weight loss were seen in rats at doses ≥ 50 mg/kg SC and in dogs at 100 mg/kg SC, potentially secondary to injection site discomfort. Local tolerance was influenced by deoxycholic acid strength and dose volume, and the use of 0.9% BA as the vehicle was found to be better tolerated compared with the use of water. Maximum locally tolerated SC doses were 50 mg/kg in rats (as 1 mL/kg x 5%) and 20 mg/kg in dogs (as 1 mL/kg x 2%).

Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in rats and dogs; all used the clinical (SC) route. The pivotal studies were of appropriate duration (6 months in rats and 9 months in dogs) and used appropriate numbers of animals, and involved twice monthly administration to rotated injection sites; the same site was treated at monthly intervals, as proposed clinically. The same regimen was used in the 3 month studies. More frequent administration at the same site (fortnightly, as weekly doses to alternating sites) was investigated in studies of 4 weeks duration.

Relative exposure

Exposure ratios in selected repeat-dose toxicity studies, calculated based on plasma AUC levels and taking dosing frequency into account, are tabulated in Table 2 found below. Moderate multiples of the clinical systemic exposure level was obtained at the highest doses in the pivotal studies.

Table 2: Relative exposure in selected repeat-dose toxicity studies

Species	Study duration	Treatment frequency		Dose mg/kg	Strength	AUC_{0-last}[1] ng·h/mL	Exposure ratio[2]	
							Per dose	>1 M
Rat (SD)	4 weeks [IXB00005]	once weekly	to two alter-nating sites	5	0.5%	2895	0.3	1.3
				10	1%	6035	0.7	2.6
				50	5%	38000	4.1	17
	3 months	twice		5	0.5%	11130	1.2	2.4

Species	Study duration	Treatment frequency		Dose mg/kg	Strength	AUC_{0-last}[1] ng·h/mL	Exposure ratio[2]	
	[IXB00026]	monthly		10	1%	10745	1.2	2.3
				50	5%	34100	3.7	7
	6 months IXB00052; pivotal	twice monthly		5	0.5%	6537	0.7	1.4
				10	1%	14397	1.6	3.1
				50	5%	30992	3.4	7
Dog (Beagle)	4 weeks [IXB00006]	once weekly	to two alter-nating sets of 4 sites	5	0.5%	1845	0.2	0.8
				10	1%	3950	0.4	1.7
				20	2%	8030	0.9	3.5
	3 M [IXB00027]	twice monthly		5	0.5%	2780	0.3	0.6
				10	1%	4980	0.5	1.1
				20	2%	9540	1.0	2.1
	9 M [IXB00076; pivotal]	twice monthly		10	2%	7972	0.9	1.7
				25	5%	14255	1.6	3.1
				50	10%	25521	2.8	5.6
Human — maximum recommended clinical dose (Study ATX-101-12-32)		once monthly		(100 mg)	1%	9159	–	

M=month
(1) AUC0-last = Area under the plasma drug concentration-time curve up to last measurable drug concentration
(2) Animal:human plasma AUC0–last and animal:human plasma AUC0–last x animal:human treatment frequency; animal AUC values are for the sexes combined, obtained on the last sampling day; the human AUC value is the overall mean, combining data for formulations with and without 0.9% BA (note: these are updated values for Round 2)

Major toxicities

Systemically, treatment was well tolerated with no mortalities, effects on body weight or target organ effects evident. Notable systemic microscopic findings were limited to a glomerular lipid embolus in the kidney of one dog (out of six) treated at 50 mg/kg twice monthly in the pivotal 9 month study. An association with treatment is not definitive given the isolated nature of the finding, but it is consistent with the pharmacological action of the drug. This occurred with administration of a strength of deoxycholic acid 10 times greater (10% compared with 1%), given more frequently (twice compared with once monthly), and more times (twenty compared with. six apparently) than applicable to clinical use of Belkyra. Accordingly, clinical relevance appears to be low.

Injection site reactions were seen across all studies, with their severity dose-dependent (ranging up to marked). The no-observable effect level (NOEL) was unable to be established for the local effects. Findings included signs of pain on injection, erythema, oedema, eschar, scabbing, SC gelatinous substance (necrotic-lysed fat), epithelial hyperplasia, acute and chronic inflammation, haemorrhage, fibrosis/fibroplasia, ulceration and necrosis (including to muscle). An increase in the numbers of segmented neutrophils in treated animals was a common haematological finding and is consistent with the local inflammatory response. There was evidence of normal wound repair and healing in post-dose and post-treatment phases (including in dedicated recovery phases of 4 to 6 week duration). Local reactions can be expected with clinical use, but with lesser overall severity or incidence than those seen in animals given the use of higher strengths, doses and more frequent administration in animal studies.

A comparable local toxicity profile was demonstrated for deoxycholic acid formulated with and without 0.9% BA in a 4-week bridging study in rats.

Genotoxicity

The potential genotoxicity of deoxycholic acid was assessed using a standard Ames bacterial reverse mutation assay, an in vitro chromosomal aberration assay with human lymphocytes and an in vivo micronucleus test in rats. The conduct of studies was in accordance with the relevant ICH guideline (ICH S2 (R1)) with the compound tested to maximum recommended concentrations or to the limits of cytotoxicity in vitro, and close to the maximum tolerated dose in vivo.[2] All studies returned negative results for deoxycholic acid. As well, in silico analyses identified no structural alerts for mutagenicity.

A number of published literature reports have implicated secondary bile acids, including deoxycholic acid, in potential carcinogenesis through genotoxic mechanisms.[3] For example, dose-dependent deoxyribonucleic acid (DNA) damage was reported in human oesophageal cell lines (HET1-A and FLO-1) exposed to sodium deoxycholate (≥ 10 μM) under neutral (but not acidic) pH conditions.[4] DNA damage in human colonic carcinoma cell lines (HT-29 and HCT 116) exposed to deoxycholic acid (500 μM) has been reported, but no effects on isolated DNA at concentrations up to 1000 μM.[5] Micronuclei formation was reported in an oesophageal adenocarcinoma cell line (OE33) exposed to deoxycholic acid (50–200 μM; pH 7.4), dependent on the induction of reactive oxygen species.[6] Clastogenic effects of deoxycholic acid have not been demonstrated under in vivo conditions. The reported effects appear to be related to cytotoxicity/oxidative stress and not direct damage to DNA. None of these published studies used methodologies consistent with normal regulatory standards. The sponsor's own studies, together with consideration of the pattern of use of the product, are sufficient to allay concerns over relevant genotoxic harm.

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline: Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use S2(R1). Current Step 4 version dated 9 November 2011

[3] Hardie LJ (2008) The Genotoxicity of Bile Acids. In: Jenkins G and Hardie LJ, ed. Issues in Toxicology, Bile Acids: Toxicology and Bioactivity,. 4th ed. Leeds, UK: Royal Society of Chemistry. pp. 72–83.

[4] Jolly AJ, Wild CP & Hardie LJ (2004). Acid and bile salts induce DNA damage in human oesophageal cell lines. *Mutagenesis.* **19:** 319–324.

[5] Glinghammar B, Inoue H & Rafter JJ (2002) Deoxycholic acid causes DNA damage in colonic cells with subsequent induction of caspases, COX-2 promoter activity and the transcription factors NF-kB and AP-1. *Carcinogenesis.* **23:** 839–845.

[6] Jenkins GJ, D'Souza FR, Suzen SH, Eltahir ZS, James SA, Parry JM, Griffiths PA & Baxter JN (2007) Deoxycholic acid at neutral and acid pH, is genotoxic to oesophageal cells through the induction of ROS: The potential role of anti-oxidants in Barrett's oesophagus. *Carcinogenesis.* **28:** 136–42.

Carcinogenicity

No carcinogenicity studies were provided. This is acceptable under the relevant ICH guideline (ICH S1A) considering the pattern of clinical use (namely the small number of dosing days) and the fact that findings in adequately conducted genotoxicity and repeat-dose toxicity studies raised no particular cause for concern.[7] Epithelial hyperplasia observed in some studies is consistent with normal wound repair and is not considered to indicate a pre-neoplastic change. It is also noted that the dose of deoxycholic acid provided by Belkyra treatment is small (approximately 3%) compared to the size of the endogenous bile acid pool in humans (100 mg compared with approximately 3 g) of which deoxycholic acid is a major component.

Reproductive toxicity

Reproductive toxicity studies with deoxycholic acid covered all stages (fertility, early embryonic development, embryofetal development, and pre- and postnatal development). Numbers of animals were appropriate but some deficiencies in the timing of treatment are noted as discussed below.

Low multiples of the clinical AUC were obtained in the developmental studies in rats, while higher ratios were evident in rabbits (see Table 3, below). This difference reflected high endogenous circulating levels of deoxycholic acid in the rabbit (approximately 50 times higher than in the rat). Mean background plasma levels of deoxycholic acid in rabbits were more than 9 times higher than the clinical C_{max} at the maximum recommended human dose (9430 ng/mL compared with 1030 ng/mL).

Placental transfer and excretion in milk were not examined in any of the animal studies. Published literature was provided reporting the presence of small amounts of deoxycholic acid in human foetal serum. This is taken as evidence of foetal transfer of maternal deoxycholic acid, since the foetal gut is regarded as germ free and thus unlikely to be capable of gut microbial transformation of cholic acid into deoxycholic acid.

Relative exposure

Table 3: Relative exposure and reproductive toxicity

Species	Study	Treatment frequency	Dose mg/kg	AUC_{0-last} ng·h/mL		Exposure ratio[1]	
				Male	Female	Male	Female
Rat (SD)	Fertility & early embryonic development (IXB00024)	Once weekly	5	4180	1610	0.5	0.2
			10	6290	5780	0.7	0.6
			50	48300	27700	5	3.0
	Embryofetal development (IXB00022)	Alternate days	5	3850		0.4	
			10	5590		0.6	
			50	16100		1.8	

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline: Guideline on the need for Carcinogenicity Studies of Pharmaceuticals S1a. Current *Step 4* version dated 29 November 1995.

Species	Study	Treatment frequency	Dose mg/kg	AUC_{0-last} ng·h/mL	Exposure ratio[1]
	Pre- and postnatal development (IXB00025)	every 3rd day	5	3850	0.4
			10	5590	0.6
			50	16100	1.8
Rabbit (NZW)	Embryofetal development (IXB00023)	alternate days	10	121000	13
			20	102000	11
			30	157000	17
Human maximum recommended clinical dose (Study ATX-101-12-32)		once monthly	100 mg	9159	-

(1) animal: human plasma AUC_{0-last} (note: updated at Round 2)

No adverse effects on male or female fertility were observed in rats treated with deoxycholic acid at doses up to 50 mg/kg once weekly (relative exposure, 5 in males and 3 in females). Early embryonic development was also unaffected. The duration of the pre-mating treatment period was two weeks for both sexes. This is in line with the relevant ICH guideline (ICH S5 (R2)) for females, but not for males where a 4 week pre-mating treatment period is recommended.[8] The use of once weekly administration also raises questions over the adequacy of the exposure period. For males, the absence of histopathological and other changes in reproductive tissues in the general repeat-dose toxicity studies is considered to be sufficient to allay concerns. Adverse effects on female fertility are not expected based on consideration of normal systemic exposure to deoxycholic acid in animals and humans.

Embryofetal development studies were performed in rats and rabbits. Administration was by SC injection on alternate days in both species, constrained by local tolerability. No adverse effects on embryofetal development were observed in rats (≤ 50 mg/kg every other day; relative exposure ≤ 1.8). In rabbits, an increase in the incidence of lung intermediate lobe agenesis was observed with dosing at 30 mg/kg every second day (relative exposure = 17). This finding is considered to be a minor anomaly in the rabbit, and it coincided with significant maternotoxicity (complete suppression of maternal body weight gain over the treatment period, associated with decreased food consumption and injection site reactions). As such, the observation is considered to be secondary to maternotoxicity and not to indicate that deoxycholic acid poses a direct hazard to embryofetal development. Given the dosing regimen and the pharmacokinetic profile of the drug the effect of exposure to exogenously administered deoxycholic acid on all critical days has not been examined. This limitation is addressed by the evident safety of high endogenous circulating levels of deoxycholic acid in the rabbit.

No adverse effects on pre- or postnatal development were observed in rats treated with deoxycholic acid at up to 50 mg/kg SC every third day during gestation and lactation (relative exposure of approximately 2).

[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility S5(R2). Current *Step 4* version incorporated in November 2005)

Pregnancy classification

The sponsor proposes Pregnancy Category B1.[9] This is considered appropriate given the absence of relevant findings in the studies described above with certain limitations in the embryofetal development studies adequately addressed by other data.

Local tolerance

Two dedicated local tolerance studies were conducted in mini-pigs using strengths of up to 2%. Findings were comparable to those in rats and dogs in the general toxicity studies.

Impurities

Substance related impurities specified in the drug substance and drug product do not exceed the applicable ICH qualification thresholds (0.15% and 0.2%) and contain no structural alerts for genotoxicity. The presence of a non-ICH residual solvent is adequately justified. A leachable detected under accelerated conditions is not considered to pose a notable toxicological risk. The impurity specification is considered to be acceptable from a nonclinical perspective.

Nonclinical summary and conclusions

- The submission for non-clinical evaluation contained a satisfactory set of studies investigating pharmacology, pharmacokinetics and toxicity. All pivotal safety-related studies were GLP-compliant.
- Cytolytic activity by deoxycholic acid (≥ 0.01%) was shown against all cell types tested in vitro (including human keratinocytes, adipocytes, fibroblasts, and skeletal muscle myocytes). Cytolysis was attenuated in the presence of protein (such as collagen and bovine serum albumin), consistent with protein binding acting to reduce levels of free deoxycholic acid. Dose-dependent adipose necrosis was shown in obese rats 24 h after SC administration of deoxycholic acid into fatty tissue. The primary pharmacology studies offer support for efficacy in the proposed indication.
- Safety pharmacology studies did not reveal any significant or clinically relevant effects of deoxycholic acid on the CNS, cardiovascular or respiratory systems.
- Systemic absorption of subcutaneously administered deoxycholic acid was generally rapid in all species (rats, rabbits, dogs and humans), where it is integrated into the endogenous bile acid pool. No clinically significant pharmacokinetic drug interactions are predicted.
- Deoxycholic acid exhibited a low order of acute systemic toxicity in studies by the SC and IV routes in rats and dogs.
- Repeat-dose toxicity studies of up to 6 months duration in rats and 9 months duration in dogs using the SC route were conducted and showed no direct systemic toxicity. A glomerular lipid embolus was observed in the kidney of one dog treated at 50 mg/kg twice monthly in the pivotal 9-month study, but the clinical relevance of the finding appears low given the much more intensive treatment regimen used. Injection site reactions were seen across all studies, and included signs of pain on injection,

[9] Australian categorisation system for prescribing medicines in pregnancy - Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

erythema, oedema, eschar, scabbing, SC gelatinous substance (necrotic-lysed fat), epithelial hyperplasia, acute and chronic inflammation, haemorrhage, fibrosis or fibroplasia, ulceration and necrosis (including to muscle). There was evidence of normal wound repair and healing in post-dose and post-treatment phases. Local reactions can be expected with clinical use, but with lesser overall severity or incidence than those seen in animals given the use of higher strengths, doses or more frequent administration here.

- Most of the nonclinical studies were conducted with deoxycholic acid formulated in vehicle containing 0.9% BA. Bridging this to support the proposed preservative-free formulation, a 4-week repeat-dose study in rats indicated a comparable local toxicity profile of formulations with and without 0.9% BA.
- Deoxycholic acid was shown to be not genotoxic in the standard battery of tests. Carcinogenicity studies were not conducted, consistent with ICH guidance considering the pattern of clinical use and the absence of a particular cause for concern identified in the genotoxicity and general toxicity programs.
- Reproductive toxicity studies revealed no direct adverse effects on fertility, embryofetal development or pre-/postnatal development, although treatment periods were not fully ideal. Pregnancy Category B1 is supported.
- There are no nonclinical objections to the registration of Belkyra for the proposed indication. The evaluator recommended revisions to the draft PI but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Submental fat is a common condition and is not related to any co-morbidity. It is more common with aging and occurs in both men and women that as per sponsor comments, presents as '*an unappealing submental profile, convexity or fullness that negatively affects the satisfaction and well-being of a substantial proportion of the population'*. Not all subjects with submental fat are bothered by the condition with the sponsor reporting that '*34% of those with marked submental fat reported being bothered by their submental fat'* and therefore the morbidity associated with the condition is psychosocial.

Currently available treatments for this condition are limited and include surgical procedures performed under general anaesthetic and targeted liposuction. These currently available treatments can be associated with significant morbidity and may have a suboptimal outcome.

Belkyra presents an alternative to current treatments and has been developed as a '*potential first-in-class, adipocytolic, submental-contouring, injectable drug*' developed as a cosmetic treatment for submental fat.

Guidance

The sponsor has had extensive correspondence with regulatory agencies including the TGA, FDA and European Medicines Agency (EMA). The sponsor has used this

correspondence to clarify the data requirements for the application and whether the addition of preservative to the vials would be acceptable. While the FDA was accepting of the addition of BA as a preservative, several of the European agencies and the TGA considered that there would be issues regarding reuse and safety. The TGA requested that: 'the company would need to provide a robust clinical and scientific justification for inclusion of BA in the formulation'. The sponsor was also advised that two pivotal efficacy studies would be required in support of efficacy. There was also regulatory advice on using questionnaires to assess psychological impact.

Contents of the clinical dossier

The data represented a full clinical development program for the indication of submental fat. The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies
- 3 dose-finding studies
- 5 supportive studies, including:
  - 2 efficacy/safety studies
  - 1 open-label, long term follow up study
  - 2 other long term follow up studies
- 1 population pharmacokinetic analysis
- 4 studies evaluable for safety only
- 4 studies designed to validate efficacy and safety outcome measures
- 1 Integrated Summary of Efficacy (ISE) and 1 Integrated Summary of Safety (ISS)

In addition, the clinical dossier contained a clinical overview and summaries of clinical efficacy and safety.

Paediatric data

This submission did not include paediatric data.

The sponsor has been granted a waiver for a Paediatric Investigation Plan in the European Union (EU) on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The sponsor has also been granted a waiver by the FDA on the grounds that the drug product does not represent a meaningful therapeutic benefit over existing treatments for paediatric patients and the drug product is not likely to be used in a substantial number of paediatric patients.

Good clinical practice

The clinical studies presented in the submission are stated to have been conducted, and appear to have been conducted according to GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

The following table lists the studies providing pharmacokinetic data in this submission.

Table 4: Summary of studies providing pharmacokinetic data

Pharmacokinetic topic	Subtopic	Study ID
Pharmacokinetics in healthy adults	General pharmacokinetics (Single dose)	Study 08
		Study 30
		Study 32
		Study 18
		Study 24
Population pharmacokinetic analyses	Target population	Study KYTH-01-13

Evaluator's conclusions on pharmacokinetics

The sponsor has adequately characterised the pharmacokinetics of deoxycholic acid. Following SC administration to submental fat of doses up to 200 mg there was increased exposure to deoxycholic acid for 24 hours. There was considerable variability in baseline deoxycholic acid concentrations. There was greater systemic exposure to deoxycholic acid with the BA free formulation.

Population pharmacokinetics

The modelling and simulation process supports the sponsor's claims with regard systemic exposure to deoxycholic acid. Deoxycholic acid concentrations return to baseline by 24 hours post-dose and accumulation is unlikely.

Please see the Extract of the CER (Attachment 2), for more details.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 below summarises studies providing pharmacodynamic data. Note none of these studies had deficiencies that excluded their results from consideration.

Table 5: Summary of studies providing pharmacodynamic data

Pharmacodynamic topic	Subtopic	Study ID
Primary Pharmacology	Effect on adipokines	Study 18
Secondary Pharmacology	Effect on QTc[1]	Study 24

(1) QTc = Corrected QT interval

Evaluator's conclusions on pharmacodynamics

The pharmacodynamic data indicated that deoxycholic acid did not have an adverse effect on lipid profiles or lipid metabolism. There was no indication of an adverse effect on QTc interval.

Dosage selection for the pivotal studies

Studies providing dosage finding data

The submission included data from 3 dose-finding studies: Study 03, Study 07 and Study 15.

Evaluator's overall conclusions on dose selection

The results of Study 03 and Study 07 were confusing and although the results indicated a treatment effect for deoxycholic acid, they did not indicate any dose effect. However, Study 15 was useful in indicating better efficacy for the 2 mg/cm^2 group. This study was also useful in developing the outcome measures used in the subsequent pivotal studies. Overall, the dose finding studies supported taking the following dose regimen through to the pivotal studies: deoxycholic acid (BA formulation) up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%) every 4 weeks.

Efficacy

Studies providing efficacy data

The data represented a full clinical development program for the indication of submental fat. This submission contained the following studies suitable for evaluation of clinical efficacy:

- 2 pivotal efficacy and safety studies (Study 22 and Study 23) using a BA-containing formulation
- 5 supportive studies including:
  - 2 other efficacy and safety studies (Study 16 and Study 17) using a BA-free formulation
  - An open label, long term follow-up study (Study 26)
  - 2 long term follow-up studies (Study 12 and Study 1403740)
- An Integrated Summary of Efficacy (ISE)

In addition, this submission contained 4 studies (Study 11, Study 20, Study 21 and Study 25) designed to validate the efficacy and safety outcome measures used in the above studies.

Studies 22 and 23 (both pivotal studies) were multicentre, randomised, double blind, placebo controlled, parallel group safety and efficacy studies. Active treatment consisted of deoxycholic acid (BA containing formulation) administered up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%), up to 50 x 0.2 mL injections, 1.0 cm grid and was administered via SC injection into submental fat for up to 6 treatment sessions every 4 weeks. The primary endpoints were the composite clinical-reported (CR) and patient-reported (PR) Submental Fat Rating Scale (SMFRS) 1-grade and 2-grade responder rates. Other efficacy measurements included submental fat volume on magnetic resonance imaging (MRI), calliper measured submental fat thickness and patient-based questionnaires.

Studies 16 and 17 (supportive studies) were multicentre, randomised, double blind, three-arm placebo controlled, parallel group safety and efficacy studies and both were similar in design. Active treatment consisted of deoxycholic acid (BA free formulation) administered at two doses: up to 50 mg, 1 mg/cm^2, 5 mg/mL (0.5%) and up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%). Both involved dosage regimens of up to 50 x 0.2 mL injections using a

1.0 cm grid and administered via SC injection into submental fat for up to 4 treatment sessions every 4 weeks. The primary endpoints were the proportions with CR-SMFRS 1-grade responder rate and Subject Self Rating Scale (SSRS) responder (score ≥ 4) rate. Other efficacy measurements included submental fat volume on MRI, calliper measured submental fat thickness and patient-based questionnaires.

For a more comprehensive overview of efficacy, please see Attachment 2.

Evaluator's conclusions on efficacy

The pivotal studies demonstrated that deoxycholic acid was superior to placebo in reducing submental fat. In Study 22, using the dosing regimen proposed by the sponsor, there was a statistically and clinically significant decrease in submental fat. There was improvement in the severity of submental fat using severity scales: 179 (70.0%) in the 2 mg/cm^2 group and 47 (18.6%) in the placebo had a composite 1-grade improvement in submental fat; 34 (13.4%) in the 2 mg/cm^2 group and none in the placebo had a composite 2-grade improvement in submental fat. There were 48 (51.10%) subjects in the 2 mg/cm^2 group and five (5.1%) in the placebo group with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS (least-squares) mean (95% confidence interval (CI)) change in submental fat thickness as measured by MRI was -18.4% (20.7% to -16.0%) for the 2 mg/cm^2 group and 0.9% (-1.4% to 3.2%) for the placebo group. The change in submental fat thickness measured by callipers was -25% in the 2 mg/cm^2 group and -7.5% in the placebo group; however there was no resulting increase in skin laxity.

In Study 23 for composite 1-grade SMFRS responders there were 171 (66.5%) in the 2 mg/cm^2 group and 57 (22.2%) in the placebo group and for composite 2-Grade SMFRS responder there were 48 (18.6%) in the 2 mg/cm^2 group and eight (3.0%) in the placebo group. There were 45 (40.2%) subjects in the 2 mg/cm^2 group and six (5.2%) in the placebo group with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS mean (95% CI) change in submental thickness measured by MRI, was -8.5% (-11.0% to -6.1%) for the 2 mg/cm^2 and 1.3% (-1.1% to 3.6%) for the placebo group. The change in submental thickness measured by callipers was -22% in the 2 mg/cm^2 group and -8% in the placebo group. There was no resulting increase in skin laxity.

The pooled analysis of the pivotal studies found the mean percentage change in MRI volume of submental fat at Visit 9 was -8.87% in the 2 mg/cm^2 groups and 1.51% in the placebo groups. The mean percentage change in calliper thickness of submental fat at Visit 9 was -19.9% in the 2 mg/cm^2 groups and -7.3% in the placebo groups.

The studies performed using the BA free formulation (Study 16 and Study 17) also supported the choice of a 2 mg/cm^2 dosing regimen over the 1 mg/cm^2 dosage regimen. Although performed with a different formulation and fewer treatment sessions, these studies also supported efficacy.

The long-term follow-up studies demonstrated maintenance of effect for up to 4 years: Study 26 for 1 year; Study 12 for 4 years and Study 1403740 for 2 years.

The pivotal studies were conducted in a population similar to that identified in the product information document. There were few subjects older than 65 years and these patients may be considered unsuitable for this treatment. The study population was generally healthy but had a higher BMI than the general population. There were no subgroup characteristics that influenced efficacy.

The studies were appropriately designed. The outcome measures were developed and validated by the sponsor. These measures were appropriate for demonstrating efficacy however the necessity for the sponsor to develop definitions and measures in order to

perform the studies reflects that the indication has not been identified as a disease. The studies were appropriately powered and the statistical tests were appropriate.

Safety

Studies providing safety data

This submission contained the following studies suitable for evaluation of clinical safety:

- 2 pivotal efficacy and safety studies (Study 22 and Study 23) using a BA-containing formulation
- 5 supportive studies including:
  - 2 other efficacy and safety studies (Study 16 and Study 17) using a BA-free formulation
  - 1 open label, long term follow-up study (Study 26)
  - 2 long term follow-up studies (Study 12 and Study 1403740)
- 4 studies evaluable only for safety (Study 04, Study 05, Study 10 and Study 19)
- An Integrated Summary of Safety (ISS).

No pivotal studies were included assessing safety as the primary outcome. The pivotal efficacy, dose response and non-pivotal efficacy studies safety data were collected for adverse events (AEs), treatment-emergent adverse events (TEAE), laboratory tests and vital signs.

For a full evaluation of safety issues with potential for major regulatory impact please refer to Attachment 2.

Patient exposure

The sponsor states in the ISS submitted for evaluation that 1,549 subjects have been treated with Belkyra for the indication of submental fat. There were 1050 subjects treated with the dose proposed for marketing of 2 mg/cm^2 and 424 subjects exposed to six doses of 2 mg/cm^2. In terms of overall exposure, there were 1172 females and 377 males; 16 subjects were aged ≥ 65 years and none aged < 18 years. There were 1334 White, 22 Asian, 98 Black and 95 subjects of other race groups. There were 301 subjects exposed to 1 mg/cm^2, 1050 to 2 mg/cm^2 and 198 to > 2 mg/cm^2. Exposure was limited to up to 6 consecutive treatment sessions with approximately 4-week treatment free intervals. Two subjects were exposed during pregnancy.

For the pivotal studies 256 subjects were exposed to 2 mg/cm^2 with 164 (64.1%) exposed to all six treatment episodes in Study 22 and 258 subjects were exposed to 2 mg/cm^2 with 140 (54.3%) exposed to all six treatment episodes.

For the supportive studies using BA free formulations, Study 16 included 121 subjects exposed to 2 mg/cm^2 with 87 (71.9%) exposed to all four treatment episodes. Study 17 included 122 subjects exposed to 2 mg/cm^2 with 90 (73.8%) exposed to all four treatment episodes.

Safety issues with the potential for major regulatory impact

In the ISS nerve injury was reported in 19 (3.7%) subjects treated with deoxycholic acid and in one (0.2%) treated with placebo. In Study 22 nerve injury was reported in 10 subjects in the 2 mg/cm^2 group and none in the placebo group. All episodes resolved. In

Study 23 nerve injury was reported in 11 subjects in the 2 mg/cm^2 group and two in the placebo. All episodes resolved.

In the ISS dysphagia was reported in 10 (1.9%) subjects treated with deoxycholic acid and one (0.2%) treated with placebo.

In the ISS urticaria was reported in five (1.0%) subjects treated with deoxycholic acid and three (0.6%) treated with placebo; however, serious skin reactions were not identified as a safety issue in the data.

Liver toxicity, haematology toxicity, cardiovascular safety or unwanted immunological events were not identified as safety issues in the data.

For a full evaluation of safety issues with potential for major regulatory impact please refer to Attachment 2.

Post-marketing data

No post-marketing data was included with this submission.

Evaluator's conclusions on safety

- Virtually all subjects treated with deoxycholic acid reported TEAEs and these were predominantly administration site related and can therefore be considered to be treatment associated. In the pivotal studies around 70% of subjects reported administration site pain, 65% reported injection site anaesthesia and more than 50% reported injection site oedema. Approximately 4% reported nerve injury, which subsequently resolved.
- In the supportive studies the frequency of administration site reactions was not related to concentration however the intensity of administration site pain increased with increasing concentration.
- The frequency and intensity of administration site reactions were similar for BA containing and BA free formulations.
- There were few long term adverse effects in the long-term follow-up studies.
- There were four deaths in the development program none of which were attributed to treatment.
- There were few serious adverse events (SAE). There was no pattern for the SAEs that might suggest any treatment effect.
- Discontinuation due to adverse events (DAE) was uncommon but most of the DAEs were administration site related. Most subjects appear to have willing to continue with treatment in spite of the very high rate of administration site TEAEs. The completion rate for studies using the 2 mg/cm2 dose level was 86.5%.
- Laboratory test abnormalities were evenly distributed between deoxycholic acid and placebo. Vital signs were not abnormal in the deoxycholic acid groups relative to placebo.

First round benefit-risk assessment

First round assessment of benefits

Deoxycholic acid, using the dosing regimen proposed for marketing by the sponsor, reduces the amount of submental fat. This was demonstrated by the sponsor using

multiple outcome measures. The pivotal studies demonstrated that deoxycholic acid was superior to placebo in reducing submental fat.

In Study 22, using the dosing regimen proposed by the sponsor there was a statistically and clinically significant decrease in submental fat. There was improvement in the severity of submental fat using severity scales: 179 (70.0%) in the 2 mg/cm^2 group and 47 (18.6%) in the placebo had a composite 1-grade improvement in submental fat; 34 (13.4%) in the 2 mg/cm^2 group and none in the placebo had a composite 2-grade improvement in submental fat. There were 48 (51.10%) subjects in the 2 mg/cm^2 group and five (5.1%) in the placebo group with a ≥ 10% reduction in MRI determined submental volume from baseline. The LS mean (95% CI) change in submental fat thickness measured by MRI was -18.4% (-20.7% to -16.0%) for the 2 mg/cm^2 group and 0.9% (-1.4% to 3.2%) for the placebo group. The change in submental thickness measured by callipers was -25% in the 2 mg/cm^2 group and -7.5% in the placebo. There was no resulting increase in skin laxity.

In Study 23 for composite 1-grade SMFRS responder there were 171 (66.5%) in the 2 mg/cm^2 group and 57 (22.2%) in the placebo group and for composite 2-grade SMFRS responder there were 48 (18.6%) in the 2 mg/cm^2 group and eight (3.0) in the placebo group. There were 45 (40.2%) subjects in the 2 mg/cm^2 group and six (5.2%) in the placebo with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS mean (95% CI) change in submental fat thickness measured by MRI was -8.5% (-11.0% to -6.1%) for the 2 mg/cm^2 and 1.3% (-1.1% to 3.6%) for the placebo group. The change in submental fat thickness, measured by callipers, was -22% in the 2 mg/cm^2 group and -8% in the placebo group. There was no resulting increase in skin laxity.

There was no apparent difference in efficacy between BA containing and BA free formulations.

The measured change in the objective measures of the amount of submental fat was less than would be expected from the changes in rating scales. The pooled analysis of the Pivotal studies found the mean percentage change in MRI volume of submental fat at Visit 9 was -8.87% in the 2 mg/cm^2 groups and 1.51% in the placebo groups. The mean percentage change in submental thickness measured by callipers at Visit 9 was -19.9% in the 2 mg/cm^2 groups and -7.3% in the placebo groups.

There were limited efficacy data in subjects aged >65 years and in non-White populations.

First round assessment of risks

Deoxycholic acid in the proposed usage has a favourable safety profile. There were few deaths or SAEs and, apart from some local reactions, these were not attributable to the treatment. The treatment is clearly a painful process but most subjects appear to have been willing to continue with treatment in spite of the very high rate of administration site TEAEs. The completion rate for studies using the 2 mg/cm^2 dose level was 86.5%.

Virtually all subjects treated with deoxycholic acid reported TEAEs and these were predominantly administration site related and can therefore be considered to be treatment associated. In the pivotal studies around 70% of subjects reported administration site pain, 65% reported injection site anaesthesia and more than 50% reported injection site oedema. Approximately 4% reported nerve injury, which subsequently resolved.

In the supportive studies the frequency of administration site reactions was not related to concentration however the intensity of administration site pain increased with increasing concentration.

The frequency and intensity of administration site reactions were similar for BA containing and BA free formulations.

There were few long term adverse effects in the long-term follow-up studies.

There were limited safety data in subjects aged over 65 years and in non-White populations.

First round assessment of benefit-risk balance

The benefit-risk balance of deoxycholic acid, given the proposed usage, is favourable.

In the opinion of the evaluator, submental fat is not a disease and deoxycholic acid in the proposed usage is a cosmetic treatment. The sponsor has not demonstrated that submental fat causes sufficient distress to result in physical or psychological harm. In the context of a cosmetic treatment however, the sponsor has demonstrated that deoxycholic acid is efficacious and has an acceptable tolerability for the subjects undergoing treatment. The sponsor has also defined an appropriate treatment regimen.

First round recommendation regarding authorisation

Deoxycholic acid (Belkyra) 10 mg/mL, solution for injection, glass vial, should be approved for the proposed indication:

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

Clinical questions

Efficacy

Q1. Does the sponsor intend to obtain further efficacy data in patients aged > 65 years?

Q2. Does the sponsor intend to obtain further efficacy data in populations other than White?

Safety

Q3. Does the sponsor intend to obtain further safety data in patients aged > 65 years?

Q4. Does the sponsor intend to obtain further safety data in populations other than White?

Q5. Does the sponsor intend to conduct extended long term follow-up studies to monitor the effects of aging in patients who have received deoxycholic acid for submental fat?

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

The benefit-risk balance of deoxycholic acid (Belkyra) given the proposed usage is favourable.

In the opinion of the evaluator, submental fat is not a disease and deoxycholic acid in the proposed usage is a cosmetic treatment. The sponsor has not demonstrated that submental fat causes sufficient distress to result in physical or psychological harm. In the

context of a cosmetic treatment however, the sponsor has demonstrated that deoxycholic acid is efficacious and has an acceptable tolerability for the subjects undergoing treatment. The sponsor has also defined an appropriate treatment regimen.

Second round recommendation regarding authorisation

Deoxycholic acid (Belkyra™) 10 mg/mL, solution for injection, glass vial, should be approved for the proposed indication:

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

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) EU-RMP Version 1.0 (dated 6 January 2015, Data-lock point: 24 March 2014) and Australian-specific annex (ASA) Version 2.0 (dated 9 October 2015, DLP 24 March 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 6 below.

Table 6: Ongoing safety concerns for Belkyra

Summary of safety concerns	
Important identified risks:	Injection site nerve injury Injection site skin ulceration
Important potential risks:	Use in patients or for conditions or with doses not yet studied
Missing information:	None

Evaluator's comment of safety specification

The RMP does not identify as important missing information safety in patients either < 18 years of age or > 65 years of age. These populations were not represented in the clinical trials and may be at risk of more severe local effects due to the effects of growth or aging.

Pharmacovigilance plan

The sponsor proposes to monitor these safety issues using 'routine pharmacovigilance and monitoring of adverse drug reactions (ADR) from the Marketing Authorisation Holder's (MAH) database'. The sponsor also intends to address the Important Identified Risks by giving detailed dosing and administration information in the product information and by conducting a Healthcare Professional (HCP) training program.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities.

The sponsor has proposed additional risk minimisation activities to mitigate the identified risks of injection site nerve injury and injection site skin ulceration, namely a health care professional training program and survey.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the TGA's evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the	The sponsor has considered the relevance for the RMP of all safety considerations raised in the Nonclinical and Clinical Evaluation Reports. All of the clinical evaluator comments relevant to the RMP have been addressed. The sponsor does not believe that any nonclinical safety issues have been raised that would result in further revisions to the RMP.	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
issue in the RMP.		
Any ASA updates should be provided in the current ASA format.	The sponsor has updated the RMP to comply with the current ASA format and has assigned a version number.	This is considered acceptable in the context of this application.
The ASA should be assigned a version number.	The sponsor has updated the RMP to comply with the current ASA format and has assigned a version number.	As above.
The sponsor should supply all of the proposed materials related to additional risk minimisation activities, including but not limited to the missing modules of the proposed health care professional training program.	A revised HCP training program presentation, based on a similar training program offered in the US and Canada, as well as the proposed injection training video and questionnaire to be administered post-training, specifically measure of effectiveness have been supplied including the training program/questionnaire and the injection video as an example from the US training program.	The original sponsor submission did contain modules 2, 3, and 5 of the then proposed health care professional training program. Modules 1 and 4 (and potentially other modules) were missing. The sponsor should state which topic areas the missing modules contain and submit them.
'Injection site anaesthesia/paraesthesia' should be added as an Important Identified Risk.	'Injection site anaesthesia/paraesthesia' has been added to the RMP as an Important Identified Risk.	This is considered acceptable in the context of this application.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
'Injection site bleeding' should be added as an Important Identified Risk.	Although there were very few verbatim reports of 'bleeding', 'injection site bleeding' has been added to the RMP as an Important Identified Risk. Additionally, in response to RMP requests, a statement has been added to the PI regarding injection site bleeding and patients who have risk factors for bleeding events.	As above.
'Injury of structures at or near the injection site' should be added as an Important Potential Risk.	'Injury of structures at or near the injection site' has been added to the RMP as an Important Potential Risk.	As above
'Dysphagia' should be added as an Important Potential Risk.	Since a small number of cases were reported in clinical trials, the sponsor considers dysphagia to be an identified risk. Therefore, 'Dysphagia' has been added to the RMP as an Important Identified Risk.	As above.
'Infections' should be added as an Important Potential Risk.	As with any elective injection procedure, treatment with Belkyra is contraindicated for patients with infection in the treatment area. Further, no post-treatment infections were observed during the clinical trials in Belkyra or placebo patients. Given that standard medical practice acknowledges that any injection procedure has the potential for infection, the sponsor does not believe it is warranted to include this event as an Important Potential Risk.	As above.
'Use in pregnancy' should be added as Missing Information.	'Use in pregnancy' has been added as Missing Information.	As above.
'Use in lactation' should be added as Missing	'Use in lactation' has been added as Missing Information.	As above.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Information.		
'Use in conjunction with other cosmetic injectables (such as botulinum toxin) should be added as Missing Information.	'Use in conjunction with other cosmetic injectables (such as botulinum toxin)' has been added as Missing Information. Additionally, the planned post-approval registry study (discussed in the response below) will collect information on concomitant use of Belkyra with botulinum toxin (same or different treatment area).	As above.
The safety concern 'Use in patients or for conditions or with doses not yet studied' should be renamed 'Off-label use'.	The RMP has been updated to reflect the safety concern 'Off-label use'.	As above.
The sponsor should provide a summary of the pre- and post-market experience of Belkyra used in conjunction with local anaesthetic.	In pivotal Phase III Studies 22 and 23, local anaesthesia (topical or injectable lidocaine) could be utilised at the discretion of the investigator (with or without ice) and was used in 47% and 70% of the overall treatment sessions, respectively, in each study. Based on this substantial experience, there did not appear to be any safety issues associated with the use of Belkyra with local anaesthetic. However, since the use of local anaesthetic was neither systematically applied nor required, it was not possible to conduct a meaningful evaluation of patient comfort associated with its use. Therefore, the sponsor conducted an exploratory Study ATX-101-13-36 (Study 36) to evaluate patient comfort associated with pain management paradigms and to understand common measures that could be taken to reduce pain. Study 36, A single-centre, double-blind, parallel-group, 2-factor patient experience management study of deoxycholic acid injection for the reduction of localised SC fat in the submental Area, enrolled a total of 83	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	subjects divided into 4 different pain management paradigms: 1) subjects received a cold pack applied to the treatment area; 2) in addition to cold pack application, subjects were treated with topical lidocaine and injectable lidocaine with epinephrine; 3) in addition to the interventions of paradigm 2, subjects also received loratadine and ibuprofen; and 4) the same interventions as in paradigm 3 plus application of a chin strap. The results of Study 36 indicated that in most patients, regardless of paradigm, post-treatment pain was mild at peak intensity and predominantly described as 'tender' by 4 hours. Swelling was modest, and bruising and induration were confined to the treatment area. Although this study had a limited number of subjects, the data suggest that a combination of ice, topical lidocaine/injectable lidocaine with epinephrine, and ibuprofen was most effective in the management of pain with average peak pain reduction close to 40%. The inclusion of epinephrine in paradigms 2-4 appeared to mitigate bruising to a modest extent. Based on the results of this study, the sponsor recommends the use of an ice cold pack for all patients prior to and after injection with Belkyra, and the optional addition of oral ibuprofen and/or a locally injected anaesthetic prior to treatment if further pain mitigation is deemed necessary by the treating physician. No post-market experience is available at this time.	
The sponsor should provide a summary of the pre- and post-market experience of Belkyra used in conjunction with botulinum toxin.	The sponsor does not have data on pre- or post-market experience with Belkyra used in conjunction with botulinum toxin. As mentioned in the response above, the planned post-approval registry study will collect information on concomitant use of Belkyra with botulinum toxin (same or different treatment area) and data will be assessed once available.	The sponsor's response has been noted.
The sponsor	As part of pharmacovigilance reporting, the	The sponsor's

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
should consider conducting a drug utilisation study to characterise the risk of off-label use further in a real-life setting.	sponsor will evaluate any safety issues that are associated with off-label use of Belkyra. In addition, the registry study discussed below in the response to RMP requests will capture additional safety information on any off-label use of Belkyra in patients who are also undergoing treatment for submental reduction.	response has been noted.
The sponsor should consider conducting a registry study to evaluate all safety concerns further in a real-life setting.	The sponsor is conducting a registry study in the US and Canada (target n = 1000) to capture safety information and clinical outcomes associated with the use of Belkyra in a real-life setting. The registry is a prospective, observational, multi-centre study that has been designed to develop a comprehensive understanding of the condition of submental fullness due to submental fat, how it is treated in current clinical practice, and the risks and benefits associated with its treatment. In addition to the collection of data on patients being treated for submental fullness, data on Belkyra treatment to other areas of the body will also be collected. The objective of this registry study will be accomplished through the systematic collection of data on the following: Practice patterns of physicians with patients who have submental fat concerns; the population of patients who are eligible for submental reduction treatment; eligible patients who elect submental fat reduction treatment; treatment procedures; treatment outcomes; safety profile through adverse event reporting of the submental reduction treatments administered; information on treatment of other areas of the body in addition to submental fat. Pending local marketing approval of Belkyra, the sponsor proposes to expand this registry study to Australia to collect the same type of real-world information. Considering RMP requests regarding drug utilisation and registry studies, respectively, it should be emphasised that the sponsor believes that it is important to assess the total safety information available	There is no definite objection to the approach outlined by the sponsor. However, there is not enough information provided to evaluate this approach in detail. Consequently, the sponsor should provide a study protocol for this registry study. Furthermore, the sponsor should outline how this registry study will capture off-label use.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	for Belkyra, including serious adverse events (SAEs) and off-label use reported globally, in order to better understand the product in clinical practice. Combining information from the planned registry, which currently targets 1000 North American patients, with comprehensive pharmacovigilance monitoring activities such as spontaneously reported post-marketing AEs, AEs reported from ongoing clinical trials, and subsequent signal detection analyses, will provide an even more comprehensive view of the safety profile of Belkyra. Further, the global safety database is configured to flag any AEs related to off-label use, so these events can be analysed separately. Healthcare professionals training programs in place for the US, Canada, and proposed for Australia comprise the same core educational material, including instruction on the critical cervicomental anatomy, mechanism of action of injected exogenous deoxycholic acid, Phase III clinical data supporting the safe and efficacious use of Belkyra, selection and evaluation of patients, proper injection technique, and patient comfort management. Therefore, information from the entire North American and Australian pharmacovigilance and registry activities should be considered when assessing on-label and off-label concerns.	
The sponsor should clarify which health care professionals are qualified to use this product and how this requirement will be enforced (for example, with a controlled distribution program).	Healthcare professionals are those who are registered as healthcare practitioners in Australia and who in the course of their professional activities may prescribe, dispense, recommend, supply or administer prescription medicine. This may include physicians, nurse practitioners, or any other person who is legally qualified to administer a prescription drug product in Australia. In order to be qualified to use Belkyra, HCPs will be required to complete web-based training and successfully pass a detailed, rigorous questionnaire prior to purchasing the product. A robust understanding of the injection training materials is necessary for respondents to	Belkyra should only be prescribed and administered by medical practitioners. Furthermore due to its status as a first in class new chemical entity with potential for incorrect administratio

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	pass the questionnaire; a 70% comprehension rate is deemed as acceptable to pass the questionnaire. Achieving a < 70% overall score on the questionnaire will require HCPs to retake web-based training. Additionally, the average performance of each questionnaire item will be assessed annually. For individual items with a score of less than 70% correct on average across all respondents, training materials related to that item will be enriched to better articulate that item's learning objective. All changes to training materials as well as the scoring for each questionnaire item will be documented in the RMP. Live training may be offered, but only to supplement comprehensive web-based training. If an HCP cannot pass web-based training, live training is not sufficient to allow purchase of Belkyra. Physicians will not be allowed to purchase product unless they 1) complete web-based training, and 2) successfully pass the training questionnaire. Additional details regarding controlled distribution may be found in response to further RMP requests below. An overview of the web-based training is provided: HCPs will understand the contributions of the cervicomental region to the full facial aesthetic. HCPs will be educated on important external anatomic landmarks and objective measurement angles. HCPs will identify key internal anatomic structures, including the platysma and submental fat compartment, and will review the typical course of the marginal mandibular nerve relative to external landmarks. HCPs will understand the characteristics of deoxycholic acid and its biologic role, pharmacologic uses of deoxycholic acid, and the mechanism of action of Belkyra. The expected onset and duration of effect, tissue response, and histology will be delineated. HCPs will understand the Phase III clinical data supporting the safe and efficacious use of Belkyra in the treatment of submental	n, this medicine should be restricted to medical practitioners that are fellows of the Royal Australasian College of Surgeons (RACS). This would need to be reflected in the controlled distribution program, that is, restricted supply to RACS fellows only. There is no objection for RACS trainees to administer this medicine under appropriate supervision by a RACS fellow. However, the medicine should only be supplied to the RACS fellow. The provided education materials are not sufficient to educate medical practitioners that do not already possess a good understanding

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	fullness associated with submental fat. The training materials will reinforce training only in the labelled indication and specify that safe and effective use has not been established outside of the submentum. HCPs will understand who the appropriate Belkyra patient is, how to evaluate and define the treatment area, and how to safely inject the product. HCPs will learn strategies to manage patient expectations and comfort during and following treatment with Belkyra to support adherence to and achievement of desired aesthetic goals. The sponsor believes that this training program will be sufficient to ensure that only appropriately qualified HCPs will be allowed to purchase Belkyra.	of the relevant anatomy. So-called cosmetic physicians or other medical practitioners without formal evidence of sufficient familiarity with head and neck anatomy should not be able to prescribe or administer this product, and subsequently should not be supplied with it.
The HCP training program should include the indications and contraindications for Belkyra. Furthermore, the program should include information on assessing causes of submental swelling for which Belkyra is not an appropriate treatment option.	The training program includes the indications and contraindications for Belkyra. Additionally, training includes an overview of the causes of submental swelling for which Belkyra is not an appropriate treatment option.	The sponsor's response has been noted. The education materials will be reviewed again after a final PI is available.
A rudimentary understanding of the training	A comprehensive training program has been created for Belkyra. Please see the above responses for a description of the	As above.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
materials is not considered sufficient to indicate successful completion of the training program. The sponsor should address this issue.	questionnaire proposed as a measure of effectiveness of training materials. Also, please see proposed questionnaire that has been provided that has been updated to reflect the content of the training materials.	
The education program should be accredited by a relevant Australian Learned College. Due to its importance, it is recommended to the Delegate that formulation of an education program and controlled distribution program acceptable to the TGA is imposed as a condition of registration for this product. Prior to approval, the sponsor should provide the TGA with the following details for agreement: All draft education materials; A clear	As described above, the sponsor intends to use completion of the comprehensive training program as a gating item to purchase Belkyra, thereby controlling distribution of the product. HCPs will not be allowed to purchase Belkyra until they have completed a web-based training program and have successfully passed a detailed, rigorous questionnaire prior to purchasing the product. In order to participate in the web-based training, each HCP is assigned a unique password and information for how to access the training. Upon completion of web-based training, the HCP must successfully pass a detailed training questionnaire that covers the most important concepts from the training. Then, a Belkyra representative will review the electronic training records to confirm training has been completed, and the HCP has passed the questionnaire (≥ 70% passing rate). If the records are complete, a report is electronically transferred to the distributor, which triggers the ability of the physician to purchase product. Even if the physician has successfully completed training, he/she may not purchase product until the distributor has received a record of his/her training completion. As an additional risk minimisation activity, the effectiveness of the training program will be measured via the training questionnaire which has been revised to reflect a comprehensive understanding of the training concepts. The average performance of each questionnaire item will be assessed annually. For individual	There is no definite objection to the sponsor's approach with regard to distribution. Accreditation by a relevant Australian Learned College is not necessary at this stage, but may be reviewed in the future. The education materials and assessment item will be reviewed again after a final PI is available, as these materials may need to be modified. A prescriber checklist is needed to identify suitable patients for this product. The sponsor

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
distribution plan; and A clear plan to measure the effectiveness of the education programme as an additional risk minimisation activity.	items with a score of less than 70% correct on average across all respondents, training materials related to that item will be enriched to better articulate the learning objective. All changes to materials, as well as the scoring for each item, will be documented in the RMP. The effectiveness of the training program will also be assessed via signal trending analyses for AEs received via standard global pharmacovigilance monitoring, ongoing clinical studies, and the patient registry. The sponsor does not believe that it should be necessary for an Australian Learned College to accredit the training program. Belkyra is a novel treatment and the training program was created by medical professionals who are experts in submental anatomy and are skilled in the administration of Belkyra. A very similar training program has successfully been rolled out in the US to more than 1200 physicians. The draft training materials, including the presentation/questionnaire and US injection video are enclosed.	should provide the details (namely protocols) on how the effectiveness of the education programme will be measured.
In the 'Precautions' section, the PI should contain a statement on dysphagia and patients with pre-existing dysphagia.	The following paragraph has been included in the Precautions section of the PI: 'Subjects with current or prior history of dysphagia were excluded from clinical trials; avoid use of Belkyra in such patients as treatment may exacerbate the condition.'	This is considered acceptable for RMP purposes subject to approval by the Delegate.
In the 'Precautions' section, the PI should contain a statement on injection site bleeding and patients that have risk factors for bleeding events.	The following paragraph has been included in the Precautions section of the PI: 'Belkyra should be used with caution in patients with bleeding abnormalities or who are currently being treated with antiplatelet or anticoagulant therapy as excessive bleeding or bruising in the treatment area may occur.'	This is considered acceptable for RMP purposes subject to approval by the Delegate.
In the	The sponsor has added the following	This is

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
'Interactions with other medicines' section, the PI should contain information (or absence of information) on the use in conjunction with botulinum toxin.	sentence to the Interactions with other medicines section of the PI: 'The use of Belkyra concomitantly with botulinum toxin has not been evaluated.'	considered acceptable for RMP purposes subject to approval by the Delegate.
In the 'Adverse events' section, the PI should contain information on adverse events from all relevant studies.	The Adverse Events table has been revised to include events from the randomised, controlled studies in submental fat.	This is considered acceptable for RMP purposes subject to approval by the Delegate.
In the 'Adverse Events' section, the PI should additionally present adverse events in a table that allows easy visualisation of the adverse events according to body system and frequency.	The updated Adverse Events table presents the information according to body system and frequency.	This is considered acceptable for RMP purposes subject to approval by the Delegate.
In the 'Dosage and Administration' section, the PI should contain the additional information that is currently contained in the relevant section of the FDA label for Belkyra, in	The Dosage and Administration section of the PI has been revised as requested and is now consistent with the FDA approved label.	As above.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
particular the information on platysma and post-platysmal fat.		
It is recommended to the Delegate that the draft consumer medicines information (CMI) document be revised to accommodate the changes made to the PI.	The CMI has been revised to accommodate the changes made to the PI document. The updated CMI is provided.	As above.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The committee provided advice on specific questions asked by the TGA relating to the RMP:

1. *Can the committee comment on the need for additional pharmacovigilance activities, such as a drug utilisation study, to evaluate the risk of off-label use further?*

The committee identified that off-label use is highly likely and could occur via departures from the proposed PI at several points:

- Use in children rather than in adults as indicated.
- Use in mild or extreme, rather than moderate to severe, convexity or fullness associated with submental fat. The committee noted that a clinician's distinction between 'mild/minimal' and 'moderate/prominent' convexity may differ from a patient's subjective view of their appearance. It was also noted that the patient's expectations and treatment objectives may change (become more specific and demanding) across treatment sessions.
- Use outside approved indication such as aesthetic sculpting.
- Use in fat deposits other than submental fat. The committee noted the existence of numerous media and social media items about the use of deoxycholic acid to 'melt fat from other parts of the body' such as under the eyes.
- More intensive therapy, via modification to volume per injection, injections per session and/or interval between sessions.
- Administration by health practitioners other than the prescriber.

The committee noted that as the PI advises that the number of treatment sessions needed to achieve a satisfactory response depends on the individual patient, it was unclear if use exceeding six treatments across approximately 20 weeks (as allowed in clinical trials) is

considered to be off-label use. ACSOM advised that the PI should be clarified in this regard and that the usage allowed in clinical trials should not be exceeded until further studies which assess deoxycholic acid's risks and benefits are carried out.

The committee advised that a drug utilisation study is important, particularly to address use of deoxycholic acid in sites other than submental fat, the number of treatment sessions, and administration by health practitioners other than prescribers. Such a study would also be useful to determine deoxycholic acid's effectiveness / outcomes compared to the number of treatment sessions.

The committee noted that advice on the costs and funding of any such drug utilisation study is outside of the ACSOM terms of reference.

2. *Can the committee comment on the adequacy of the proposed additional risk minimisation activities, including measures to ensure that only medical practitioners sufficiently familiar with deoxycholic acid and its use within the approved indication are able to use this product?*

The Dosage and Administration section of the proposed PI includes the following advice:

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.

The committee endorsed these statements. The anatomy of the area is complex and a thorough understanding of external and internal features and their boundaries and variability is essential for undertaking administration of deoxycholic acid. A member advised that knowledge of the facial anatomy that is critical for the administering practitioner to consider prior to injection include: palpation of the anatomical landmarks – such as mandible and hyoid bone; and delineation of submental triangle, course of marginal mandibular nerve and 'danger zone' for injection. This knowledge is needed to avoid injection close to the possible location of the marginal mandibular nerve.

Cases of marginal mandibular nerve motor neuropraxia occurred in clinical trials, with this nerve damage lasting for a median of 45 days. Such injury to the cervical and marginal mandibular branches of the facial nerve can result in compromised perioral motor function, including an asymmetric smile and facial muscle weakness. Risks of nerve damage may be higher in later treatment sessions, as existent submental fat will have relatively protected vulnerable structures during earlier treatment sessions.

The committee advised that use of deoxycholic acid should be limited to practitioners with experience in head and neck surgery (for example, head and neck surgeons (otolaryngologists) and plastic surgeons). For example, Fellows of the colleges for otolaryngology and plastic surgery could be assumed to have sufficient background knowledge and experience to be able to prescribe and administer deoxycholic acid safely. Medical practitioners without experience in head and neck surgery would require rigorous education and training, preferably accredited by a relevant specialist college; successful completion of such training should be mandatory before a practitioner can prescribe and administer deoxycholic acid.

Only medical practitioners sufficiently familiar with deoxycholic acid and its use within the approved indication should be able to prescribe this medicine. The committee was advised that the TGA has experience in making decisions that require sponsors to conduct risk management activities such as prescriber training, controlled distribution, and for supply of the medicine to be contingent on the would-be prescriber satisfying training requirements.

The committee was concerned that the incidence of adverse events could increase if unrestricted use of deoxycholic acid was permitted. Practitioners experienced with the use of botulinum toxins or liposuction may not necessarily have the appropriate skills and

experience with regard to knowledge of the facial anatomy and use of deoxycholic acid. The committee advised against administration by nurses or other health practitioners.

The committee advised that the education strategy (training questionnaire) outlined by the sponsor is inadequate to determine if a trainee possesses the adequate skills.

A thorough understanding of the anatomy will also support patient counselling and management of patient expectations. For example, only the fat in front of the platysma muscle (pre-platysmal fat) is suited to deoxycholic acid treatment and it accounts for no more than 70% of the fat in the submental area.

Apart from hypersensitivity to deoxycholic acid, the only contraindication mentioned in the PI is infection in the treatment area. ACSOM advised that this is insufficient to manage the risks of deoxycholic acid injections. Absolute contraindications need to be expanded to include: submental or cervical gland lymphadenopathy; dysphagia of unknown origin or of known upper aero-digestive tract origin; induration, swelling, inflammation in the treatment area; facial nerve paralysis, or facial nerve weakness (paresis). Relative contraindications for injections are: thyroid gland enlargement (thyromegaly); inferiorly located submandibular glands – ptosed submandibular glands; prominent platysmal bands with minimal fat excess; excessive skin laxity; scar tissue from previous trauma or surgery; prior surgical or non-surgical or minimally invasive procedures in the area of injections.

The committee also noted that the PI was silent on how long patients should remain under observation before discharge from the clinic.

Summary of recommendations

- The original sponsor submission contained Modules 2, 3, and 5 of the then proposed health care professional training program. Modules 1 and 4 (and potentially other modules) were missing. The sponsor should state which topic areas the missing modules contain and submit them.
- The sponsor should provide a study protocol for the CONTOUR registry study. Furthermore, the sponsor should outline how this registry study will capture off-label use.
- Prescription, administration and supply of Belkyra should be restricted to medical practitioners that are fellows of the Royal Australasian College of Surgeons (RACS). This would need to be reflected in the controlled distribution program or specifically restricted supply to RACS fellows only.
- The sponsor should provide the details (such as protocols) on how the effectiveness of the education programme will be measured.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval was recommended by the quality evaluator.

Nonclinical

There were no nonclinical objections to the registration of Belkyra for the proposed indication.

Clinical

Clinical efficacy

A summary of the most important Phase III studies is given in the following table.

Table 8: Summary of Phase III study designs and primary endpoints

	Studies 16/17	Studies 22/23
Location	EU	US and Canada
Formulation	Preservative-free (no BA)	Contains preservative (BA)
Treatment groups	Placebo 1 mg/cm^2 2 mg/cm^2	Placebo 2 mg/cm^2
Number of treatments	Up to 4	Up to 6
Primary endpoints	CR-SMFRS 1-grade responder rate SSRS (responder score ≥ 4)	Composite SMFRS 1-grade responder rate (CR and PR) Composite SMFRS 2-grade responder rate (CR and PR)

The formulations used in the studies were slightly different. The sponsor stated that the differences (including the BA) were not expected to affect efficacy and safety; a view endorsed by the clinical evaluator. The dosing scheme in Studies 22 and 23 (up to 6 treatments, 4 weeks apart, 2 mg/cm^2) match that in the proposed PI and these studies are therefore considered more pivotal, although they were for the formulation that included BA.

The studies were multicentre, randomised, double-blind and placebo-controlled trials.

Clinician-reported submental fat rating scale (CR-SMFRS)

The CR-SMFRS score was based on the investigator's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head.

Each investigational centre was provided with the CR-SMFRS book containing representative photographs for each score. The score was determined using the definitions in the rating scale and representative photographs associated with each score. To maintain a consistent posture from which the scores were made, the final determination of the score was made while the subject's head was in the Frankfort plane posture. Each site had a 2-inch by 2-inch (approximately 50.8 mm by 50.8 mm) grid poster that was placed on the wall with the horizontal lines parallel to the floor, in the area where

the assessments were conducted. The CR-SMFRS scoring system is shown in Table 9 below.

Table 9: CR-SMFRS interpretation

Score	Severity
0	absent
1	mild
2	moderate
3	severe
4	extreme

In Studies 16/17 (EU) the primary efficacy endpoints were reduction from baseline to Visit 7 (Visit 7 = 12 weeks after the last treatment) of submental fat as assessed by the proportion of patients who had:

- at least a 1-grade improvement on the CR-SMFRS
- at least a SSRS score of 4

In Studies 22/23 (US and Canada) the primary efficacy endpoints were reduction from baseline to Visit 9 (Visit 9 = 12 weeks after the last treatment) of submental fat as assessed by the proportion of patients who had:

- at least a 1-grade simultaneous improvement on the CR/PR-SMFRS
- at least a 2-grade simultaneous improvement on the CR/PR-SMFRS

The median age of patients in the Phase III studies was just below 50 years (patients younger than 18 years or older than 65 years were exclusions); 75% of patients were women. One difference between the studies was that the EU studies enrolled patients up to BMI of 30 whereas the Canadian/US studies enrolled patients up to BMI 40. Patients with submental fat graded as 2 or 3 by themselves or the investigator were included in the studies (patients with submental fat grades 1 or 4 were excluded).

Results for primary endpoints

Results for the primary endpoints of the most important Phase III studies is summarised in Tables 10 and 11.

Table 10: Results for Studies 16/17

	Deoxycholic acid 10 mg/mL (n = 121)	Placebo (n =122)
CR-SMFRS 1-grade responder rate	79 (65%)	28 (23%)
SSRS (responder= score ≥ 4)	80 (66%)	35 (29%)

Table 11: Results for Studies 22/23

	Deoxycholic acid 10 mg/mL (n = 256)	Placebo (n = 250)
Composite SMFRS 1-grade responder rate	179 (70%)	46 (19%)
Composite SMFRS 2-grade responder rate	34 (13%)	1 (< 0.1%)

Secondary endpoints were supportive of efficacy and did not raise any concerns.

Clinical safety

Deoxycholic acid is an endogenous substance which is present in the systemic circulation. The pharmacology studies show that levels peak one hour after injection with Belkyra at levels about 2 to 3 times higher than endogenous levels. Levels return to baseline at 12 to 24 hours after injection.

Belkyra acts locally in the SC fat and the safety profile reflects this local action. As is the case with many new medicinal products, it is not possible, based on the currently available data, to rule out long-term local or systemic adverse reactions.

About 700 patients were exposed to the dosing regimen proposed in the PI (up to 6 months).

Injection site pain occurred in about 70% of patients. Other common adverse reactions were: injection site haematoma (60%); injection site anaesthesia (60%) and injection site oedema (50%). The pain is of moderate intensity and typically resolves quickly. Overall, the adverse reactions in the administration area were manageable and reversible. To date no systemic adverse reactions have been identified.

Injury or irritation of the marginal mandibular branch of the facial nerve occurred in about 2% of patients in the Belkyra group versus 0.2% of the placebo group. It is unclear whether this higher frequency in the Belkyra group is a chance event or related to deoxycholic acid. All cases resolved without treatment. Dysphagia occurred in 2% of patients in the active arm.

Clinical evaluator's recommendation

The clinical evaluator advised the TGA that the benefit-risk balance was favourable.

Risk management plan

The following two tables summarise the safety concerns detailed in the EU-RMP and in the ASA version 2.

Table 12: Summary of safety concerns in the EU-RMP v1.0

Category	Identified safety concerns
Important identified risks	Injection site nerve injury Injection site skin ulceration
Important potential risks	Use in patients, or for conditions or with doses not yet

Category	Identified safety concerns
	studied
Important missing information	None

Table 13: Summary of safety concern in the ASA v2.0 (to apply in the Australian context)

Category	Identified safety concerns
Important identified risks	Injection site nerve injury Injection site skin ulceration Injection site anaesthesia/paraesthesia* Dysphagia*
Important potential risks	Injection site haemorrhage in patients with bleeding factors* Injury of structures at or near the injection site* Off-label use*
Important missing information	Use during pregnancy* Use during lactation* Use in patients with submental fat (SMF) grade 1 or 4* Use in patients older than 65 years* Use in patients younger than 18 years* Use in conjunction with other cosmetic products*
*added by the sponsor at the request of the TGA to the ASA; 'Off-label use' replaced 'Use in patients or for conditions or with doses not yet studied' to reflect that even though a condition or patient group was studied, this may not be part of the approved indication. To important missing information, add: the efficacy and safety of re-treatment long-term local safety long-term systemic safety	

The sponsor is proposing a registry study (CONTOUR registry) to evaluate safety further and that will also capture off-label-use. This study will include Australian patients.

An additional risk minimisation measure of prescriber education is proposed to mitigate the risk of injection site nerve; and, more generally, to define the treatment area and safely inject the product. The current materials proposed by the sponsor are considered promotional.

The educational materials are being reviewed by an independent external clinical expert, whose advice will be used to finalise the ASA of the RMP.

Belkyra was reviewed at ACSOM. The minutes will be provided to the ACPM.

Risk-benefit analysis

Delegate's considerations

The confirmatory Phase III trials met their pre-specified objective of reducing fat below the chin. Many (but not all) patients expressed their satisfaction with the outcomes. There are no data on the efficacy (or safety) of re-treatment.

The adverse reactions, identified in the pre-market data were local, reversible and manageable. A final conclusion on long-term safety or systemic safety cannot be made based on the available (pre-market) data.

It is likely that, in Australia, most administration will be by non-specialists. To ensure safe injection of the product, prescriber education is proposed.

Parts of the current educational materials, proposed by the sponsor, are considered promotional. The TGA has sought independent external clinical advice on their content. Agreement on the educational materials is required before the RMP can be finalised.

Proposed action

The Delegate had no reason to say, at this time, that Belkyra should not be approved for registration.

Delegate's issues for sponsor

1. Please provide details of the educational qualifications of the health care practitioners who administered Belkyra in the four Phase III studies.
2. Please provide details of what training and supervision was provided to the health care practitioners who administered Belkyra in the four Phase III studies.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Summary

Allergan Australia Pty Ltd refers to the Delegate's overview and request for ACPM's advice (dated 29 April 2016) and concurs with the Delegate's preliminary assessment that there is 'no reason to say, at this time, that Belkyra should not be approved for registration'. The sponsor notes the Delegate's questions to the ACPM regarding the educational qualifications of the HCPs who administered Belkyra as part of the Phase III program and the training and supervision provided to these HCPs. Allergan's response to the questions and additional comments raised by the Delegate are provided below.

Discussion of delegate's comments

Delegate's questions for the sponsor

1. *Please provide details of the educational qualifications of the health care practitioners who administered Belkyra in the four Phase-3 studies.*

Sponsor's response

In the 4 Phase III studies the investigator selection criteria specified physicians as investigators who were 'qualified by training and experience (were selected) as appropriate experts to investigate the study drug'.

Given the aesthetic nature of the indication, investigators were selected based on their training, experience, and clinical research capacity in the area of aesthetic medicine because such investigators have the understanding and experience in the treatment and management of aesthetic patients, knowledge of the relevant anatomy of the face and neck, and experience with the use of minimally invasive injectables including treatments of SC injection of the cervicomental area; hence, the investigators consisted of dermatologists, plastic surgeons, and a small number of other doctors experienced in seeing and treating aesthetic patients.

2. *Please provide details of what training and supervision was provided to the health care practitioners who administered Belkyra in the four Phase III studies.*

Sponsor's response

The sponsor conducted and documented training through live investigator training meetings, periodic webinars, and study monitoring visits. Specific to the treatment injection, investigators were required to view a standardised training video that detailed the baseline clinical and anatomic pre-treatment evaluation, marking and grid application to the target treatment area, product preparation (preparation of syringes for injection) and the injection technique as well as pre- and post-injection care of the patient.

Ongoing oversight and supervision of the study conduct, including the HCPs, was performed by medical monitors and regional clinical monitors through clinic visits and telephone follow-up.

As a result of the training provided, the outcomes of the clinical studies were consistent across the different specialties. Data from the 4 Phase III studies confirmed that there were no significant differences observed in the number of treatment sessions or volume of Belkyra injected. Safety data from the Phase III clinical studies also indicated that, in general, the types and intensities of TEAEs were similar across all specialties.

Since the completion of the 4 Phase III clinical studies, the Sponsor worked with HCPs in cadaveric anatomical dissection to better understand the anatomy of the submental region, and therefore how to avoid injections near the area of marginal mandibular nerve. This information has been incorporated into the updated PI and a post-approval training programme that is currently ongoing in the US and Canada (and proposed to be available for HCPs in Australia), which includes the external and internal anatomy of the cervicomental region as well as proper injection technique for Belkyra. As such, HCPs in the commercial setting will receive more specific information on the proper use of Belkyra than the HCPs who participated in the clinical studies, especially with respect to the likely position of the marginal mandibular nerve in relation to the submental treatment area. Post-marketing safety data indicated that submental fat treatment in both the commercial setting and the registry study in the US, administered by a broad range of qualified US physicians, have been associated with a decreasing incidence rate of injection site nerve injury as compared with the adverse event rates reported in the Phase III clinical studies.

Discussion of delegate's comments on the RMP

In the Delegate's overview, the following comment was included below Table 13 titled 'Summary of safety concern in the ASA v2.0 (to apply in the Australian context)':

Add as important missing information to the RMP:

- The efficacy and safety of re-treatment

- Long-term local safety
- Long-term systemic safety

Sponsor's response

The sponsor agrees to include efficacy and safety of retreatment, long-term local safety, and long-term systemic safety as missing information to the RMP. The applicant proposes to apply routine pharmacovigilance to collect and monitor information related to efficacy and safety of retreatment, long-term local safety, and long- term systemic safety and identify any potential long term safety signals that may be attributable to Belkyra use. In addition, Study ATX-101-08-12 (Study 12) and Study ATX-101-13-35(Study 35) are proposed as additional pharmacovigilance activities to collect additional information on maintenance of effect as well as long-term local and systemic safety. Study ATX-101-08-12 (Study 12) is a non-treatment study that collected long term follow-up data on subjects who received treatment in previous Phase II studies of Belkyra for the reduction of submental fat. The final report is anticipated in fourth quarter of 2016.

Discussion of delegate's request for information

Sponsor's response

Study ATX-101-13-35 (Study 35) is a non-treatment study that collected long term follow-up data on subsets of subjects who participated in Phase III Studies 22 and 23. The final report is anticipated in the fourth quarter of 2016.

The applicant considers that routine risk minimisation is sufficient to minimise the risks associated with retreatment or long-term use of Belkyra. Once Belkyra is approved and marketed, post-marketing reports relating to the safety concerns described in this RMP will be constantly monitored. Effectiveness of risk minimisation would be reassessed if the current assessment of the frequency or other characteristics of the safety concerns would change as a result of these ongoing pharmacovigilance activities.

Discussion of delegate's comments on educational materials

In the Delegate's overview, the Delegate makes the following comment:

> *'An additional risk minimisation measure of prescriber education is proposed to mitigate the risk of injection site nerve; and, more generally, to define the treatment area and safely inject the product. The current materials proposed by the Sponsor are considered promotional.*
>
> *The educational materials are being reviewed by an independent external clinical expert whose advice will be used to finalise the Australian annex of the RMP.'*

Sponsor's response

The sponsor acknowledges the Delegate's comment relating to the promotional nature of the proposed training material and will work with TGA to develop a training and education programme for Belkyra injection as an additional risk minimisation measure. This will help to ensure that HCPs are adequately trained and qualified in their understanding of facial anatomy and injection technique as a prerequisite to purchasing Belkyra. Allergan, as an aesthetic drug and device manufacturer, has demonstrated extensive experience in the provision of similar aesthetic products to HCPs.

The to-be-updated RMP, including the ASA, will provide measures to ensure adequate oversight of any potential safety concerns associated with Belkyra, training for HCPs and routine pharmacovigilance monitoring. In addition, the proposed PI includes sufficient information regarding directions for use and associated risks to allow for the safe use of Belkyra in the post-marketing setting. Therefore, it is reasonable that patients, in consultation with their HCPs, will be able to weigh the benefits and risks of treatment with Belkyra on an ongoing basis and decide whether or not to initiate and/or continue

additional treatment. Given the evidence from the Phase III trials, Belkyra has a clear dosing and treatment guidance for the proposed indication.

Sponsor's conclusion

Allergan concurs with the Delegate's conclusion that Belkyra should be approved for the treatment of submental fat. The sponsor acknowledges the Delegate's comments regarding the promotional nature of the educational materials and is committed to working with TGA in order to produce materials to meet any educational requirements.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Belkyra (Kybella initially proposed) solution for injection containing 10 mg/mL of deoxycholic acid to have an overall positive benefit–risk profile for the sponsor indication:

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

In making this recommendation the ACPM:

- Advised that the sponsor must submit a RMP to the satisfaction of the TGA.

Proposed PI/CMI amendments

The ACPM advised on the inclusion of the following:

- A statement in the PI under the Clinical Trials section highlighting that the investigators in the clinical trials were plastic surgeons, dermatologists and a small number of other doctors with extensive experience in administration of aesthetic treatments.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- The ACPM reiterated the importance of adequate training in product administration which should be developed to the satisfaction of the TGA prior to product approval. The ACPM acknowledged the sponsor has agreed to develop a training and education program as an additional risk minimisation measure, and at the Delegate's request, has agreed that such training should be less promotional in nature and content.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Belkyra deoxycholic acid 10 mg/mL solution for injection indicated for:

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

Specific conditions of registration applying to these goods

The deoxycholic acid European RMP (EU-RMP), Version 3.0, dated 2 May 2016 (data lock point 27 April 2016) with ASA Version 2.0, dated 9 October 2015 (data lock point 24 March 2014), to be revised to the satisfaction of the TGA must be implemented in

Australia. Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Attachment 1. Product Information

The PI for Belkyra approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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