1.0 Abstract

Title

Injectors' Survey to Assess Effectiveness of BELKYRA® (deoxycholic acid) Risk Minimisation Activities.

Keywords

BELKYRA®, additional risk minimization measures, healthcare professionals

Rationale and Background

BELKYRA® (deoxycholic acid) is approved for the treatment of moderate to severe convexity or fullness associated with submental fat in adults, particularly when this condition has a significant psychological impact on the patient. Administration of BELKYRA® should be restricted to qualified physicians, although trained healthcare professionals (HCPs) may administer BELKYRA® under physician supervision, national guidelines permitting.

As part of the European Medicines Agency (EMA) post-approval requirements for BELKYRA®, requested on 8 May 2017, the Marketing Authorisation Holder (MAH), AbbVie Inc. (having acquired Allergan Pharmaceuticals International Ltd. and merging operations as an integrated company), was required to implement risk minimisation measures (RMMs) including the introduction of educational materials to complement the product's Summary of Product Characteristics (SmPC). Consequently, the Injector's Guide for the Safe Use of BELKYRA® was introduced as an additional risk minimization measure (aRMM). The guide, which includes a patient selection checklist and procedure checklist, provides information on the recommended injection technique and how to minimise the important identified risks of injection site nerve injury and injection site skin ulceration.

The Injector's Guide for the Safe Use of BELKYRA® was distributed to HCPs who administer BELKYRA®. As part of the regulatory commitment to assess the

effectiveness of the aRMM, this survey was designed to assess the effectiveness of the Injector's Guide for the Safe Use of BELKYRA® in informing HCPs of the risks of injection site nerve injury and injection site skin ulceration.

Research Question and Objectives

The objective of this study was to assess HCPs' understanding of the key safety information on BELKYRA® regarding injection site nerve injury and injection site skin ulceration as communicated in the Injector's Guide for the Safe Use of BELKYRA®.

The primary objective of this study was to assess HCP knowledge of the risk of skin ulceration and nerve injury associated with the use of BELKYRA®. Primary endpoints included assessment of the following:

- Knowledge that caution should be exercised when using BELKYRA® in patients with inflammation or induration at the proposed injection site; symptoms of dysphagia; and prior surgical or aesthetic treatment of the submental area
- Knowledge that BELKYRA® should not be injected above the inferior border of the mandible
- Knowledge to inject BELKYRA® only within the target submental fat treatment area
- Knowledge that you should not inject BELKYRA® into post-platysmal fat; not intradermally to avoid risk of skin ulceration; and not in the "No treatment zone" to avoid injury to the marginal mandibular nerve; and not into or in close proximity (1-1.5 cm) to thyroid gland, salivary gland, lymph nodes, and muscle
- Knowledge that you must assess smiling and swelling for nerve injury and dysphagia

Secondary study objectives were to assess prescriber's knowledge of the appropriate use of BELKYRA® including indications and specifications of treatment, correct injection procedure, contra-indications and post-treatment care.

Study Design

This study was a multi-national, observational, cross-sectional survey of HCPs conducted in Spain, Italy, Sweden, Bulgaria, Lithuania, and the United Kingdom (UK).

Cognitive pre-test interviews were conducted on translated questionnaires prior to survey launch, to identify any questions that required revision based on areas of confusion or miscomprehension. Interview participants included HCPs from Italy (n=1), Spain (n=2), and Sweden (n=3) who were known to be actively treating patients with BELKYRA® and who were independent of AbbVie and ICON plc.

The survey included 22 questions: 5 screening questions to assess participant eligibility, 11 questions evaluating HCPs' knowledge of the aRMM, and 6 questions on demographics and HCP characteristics. Although it was planned to launch the survey within 12 to 18 months following the distribution of the Injector's Guide in 2019, EMA granted an extension of this timeline due to the COVID-19 pandemic, with the survey to be launched by August 2021. The survey included questions/statements to assess the HCPs' understanding of the key safety messages as outlined in the Injector's Guide for the Safe Use of BELKYRA®.

The targeted population for recruitment included HCPs able to treat patients with BELKYRA® who were practicing in a participating country. Healthcare professionals were eligible for inclusion if they were currently treating patients with BELKYRA®. Current or past employees of AbbVie or any of its affiliates, ICON plc, the EMA or any national competent authority (NCA) were excluded.

Results

Surveys were sent to 392 HCPs, of which 21 (5.4%) completed the eligibility questions, and 18 completed at least one question assessing a survey endpoint. 20 HCPs (95.2%) were eligible, while 1 (4.8%) was excluded due to employment with AbbVie or its affiliates, ICON plc, EMA, or an NCA. Of eligible participants, 18 (90.0%) answered at least one question assessing a study endpoint.

As their primary source of information other than the Injector's Guide, 7 (38.9%) respondents indicated that they rely on the Injector's Guide for the Safe Use of BELKYRA®, while other common sources included the literature (n=8, 44.4%), the summary of product characteristics (SmPC) (n=5, 27.8%), and conferences (n=5, 27.8%). Most respondents (n=10, 55.6%) had fewer than 5 years of experience performing aesthetic procedures, and the majority of respondents (n=11, 61.1%) were under the age of 40.

The gender distribution included 11 (61.1%) male and 7 (38.9%) female respondents. Participants were predominantly from Sweden (n=12, 66.7%), followed by Italy (n=4, 22.2%), with one respondent each from Spain (5.6%) and Bulgaria (5.6%). No HCPs responded to the survey in Lithuania or the UK. The most common specialty (n=7, 38.9%) was "other qualified healthcare providers under the supervision of a medical doctor." All respondents had treated patients with BELKYRA® in the previous 6 months, with half treating 1-5 patients.

All respondents (100%; 95% CI: [81.5, 100.0]) demonstrated knowledge that caution should be exercised when using BELKYRA® in patients with inflammation or induration at the proposed injection site, in patients with symptoms of dysphagia, or in patients with a history of surgical or aesthetic treatment of the submental area. Similarly, all respondents (100%; 95% CI: [81.5, 100.0]) were aware that injections should not be performed above the inferior border of the mandible. Knowledge of proper injection placement within the target submental fat treatment area was reported by 17 respondents (94.4%; 95% CI: [72.7, 99.9]). Awareness of critical injection

precautions was demonstrated by 16 respondents (88.9%; 95% CI: [65.3, 98.6]). Finally, 16 respondents (88.9%; 95% CI: [65.3, 98.6]) recognized the importance of assessing smiling and swelling for nerve injury and dysphagia.

Only 1 respondent was aware (5.6%; 95% CI: [0.1, 27.3]) that BELKYRA® is not indicated for treating mild convexity or fullness associated with submental fat. A majority (83.3%; 95% CI: [58.6, 96.4]) correctly knew not to administer BELKYRA® to obese patients or to those with body dysmorphic disorder. Six respondents (33.3%; 95% CI: [13.3, 59.0]) knew that caution does not necessarily need to be exercised in patients aged 55 and older. However, the majority (94.4%; 95% CI: [72.7, 99.9]) were aware that caution should be taken in patients with excessive skin laxity, prominent platysmal bands, or other conditions. Most knew to screen patients for other causes of submental convexity/fullness before treatment (88.9%; 95% CI: [65.3, 98.6]) and recognized that BELKYRA® cannot be used in patients with an active injection-site infection (88.9%; 95% CI: [65.3, 98.6]).

All respondents (100%; 95% CI: [81.5, 100.0]) were aware that treatment sessions should be spaced at least 4 weeks apart, though only 7 (38.9%; 95% CI: [17.3, 64.3]) correctly noted that more than four treatment sessions can be performed. Only 9 respondents (50.0%; 95% CI: [26.0, 74.0]) correctly identified that the appropriate injection volume is 0.2 ml (2 mg) per site, spaced 1 cm apart. However, 17 (94.4%; 95% CI: [72.7, 99.9]) correctly recognized that the maximum dose per session is 10 ml (100 mg, equivalent to 50 injections).

Knowledge of patient comfort measures varied, with 16 respondents (88.9%; 95% CI: [65.3, 98.6]) acknowledging that pre-treatment analgesia may be provided, but only 8 (44.4%; 95% CI: [21.5, 69.2]) recognizing that ice packs can be applied post-treatment.

All respondents (100%) reported receiving and reading the Injector's Guide for the Safe Use of BELKYRA®.

Discussion

Findings from this survey provide insights into the knowledge of HCPs regarding the safe use of BELKYRA®. However, due to a low response rate, the results may not be generalizable, as the sample size of 18 was below the targeted minimum of 75 responses. The limited sample size, along with most respondents originating from Sweden, suggest that these results may not be representative of across other geographies.

All respondents demonstrated knowledge of key safety precautions, including avoiding injection above the inferior border of the mandible and exercising caution in patients with inflammation or prior submental procedures. Most participants correctly identified the appropriate target submental fat treatment area and recognized critical safety measures such as avoiding post-platysmal fat and screening for nerve injury and dysphagia. These results suggest a high understanding of the risk of skin ulceration and nerve injury, and endpoints appear to meet the success criteria of 75% or higher. However, due to the small sample size, results should be interpreted with caution.

The secondary endpoint findings revealed gaps in knowledge regarding patient selection. Only one respondent knew that BELKYRA® is not indicated for treating mild convexity or fullness associated with submental fat. However, most respondents knew not to use BELKYRA® in obese patients or in those with body dysmorphic disorder. Additionally, while the majority were aware of the need for caution in patients with excessive skin laxity and platysmal bands, only a third knew that age alone (>55 years) is not necessarily a contraindication.

Healthcare professionals had mixed knowledge of dosing and administration specifics. While all respondents knew to space treatments at least four weeks apart, many were unaware that more than four sessions may be necessary. Only half of participants recognised the correct injection volume in each injection site, however the vast majority correctly recognized the maximum dose per session to be injected. Similarly, knowledge of measures to be taken for patient comfort was mixed. Most HCPs were

aware that pre-treatment analgesia could be provided, but less than half recognised that post-treatment ice packs may be used.

Overall, the survey results indicate high awareness among HCPs regarding the safe administration of BELKYRA®. Knowledge gaps were identified specifically in patient selection regarding severity of treatment indication, dosing recommended per each site although participants had clear knowledge of maximum dose to be injected, and patient comfort after injection. Those areas possibly require further clarification and education.