1 ABSTRACT

Title

Survey to evaluate the knowledge and understanding of the key safety messages in the Healthcare Professional guide and the patient guide for SULIQUA

Keywords

SULIQUA, Safety, Educational Materials, Healthcare Professional, Patients, Risk minimisation plan.

Rationale and background

In the Risk Management Plan (RMP) assessment report by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA-PRAC), dated 7 July 2016, the Marketing Authorisation Holder (MAH) was requested to submit key safety messages for inclusion in a Healthcare Professional (HCP) guide and a patient guide to address the potential risk of medication errors occurring at the prescribing, dispensing and patient level. The MAH was further asked to propose a study to assess the effectiveness of these additional risk minimisation measures (aRMMs), i.e. the HCP guide and patient guide. Therefore, this study was performed to evaluate the knowledge and understanding of the educational materials (EMs)/guides provided to the HCPs who prescribed or dispensed SULIQUA, and to the patient population treated with SULIQUA after its approval and launch.

Research question and objectives

Research question: Were the key safety messages in the HCP guide and the patient guide, implemented as aRMMs, effective in:

- Providing good knowledge and understanding about SULIQUA to HCPs who prescribed or dispensed SULIQUA and to patients (or their caregivers) treated with SULIQUA?
- Reducing the risk of medication errors when prescribing/delivering or using SULIQUA?

Objective: To assess the knowledge and understanding of the key safety messages in the HCP guide and patient guide among HCPs who prescribed or dispensed SULIQUA and patients (or their caregivers) treated with SULIQUA, respectively.

Study design

The study was a non-interventional, cross-sectional, multinational, multichannel survey conducted through two Web questionnaires: one to collect information from HCPs who prescribed or dispensed SULIQUA and the other for patients (or their caregivers) treated with SULIQUA, respectively.

Setting

This survey was planned to be implemented in several European countries in three waves. Due to lower than projected market penetration and slow questionnaire completion, the MAH reached out to PRAC to propose a reduced targeted sample size. Following PRAC recommendation (report issued 23 December 2019), the MAH agreed with an alternative proposal to extend the recruitment period from three to six months or even one year per wave to reach the initial estimated sample size. In addition, PRAC recommended to keep three waves of data collection to be able to reach the agreed target sample size or provide a justification for conducting two waves if it would improve feasibility of the study. However, on 29 July 2020, the MAH decided not to conduct wave 3 for the following reasons: the continued lower market penetration; no ethical submission pathway available in Italy; and the fact that the final target sample size was nearly met. Therefore, the MAH extended wave 2 for an additional period of two months. On 30 September 2020, the overall target size of 384 completed questionnaires was met. In total, wave 1 duration was of six months and wave 2 was of eight months. The strategy was agreed by the PRAC on the 25 February 2021.

The following countries were included in different study waves - wave 1: Hungary, Czech Republic, Slovenia; and wave 2: Belgium, Romania, United Kingdom (UK). Data for wave 1 were collected between September 2019 and 31 May 2020 (two months of interruption in November and December 2019). Wave 2 started on 15 January 2020 and ended on 30 September 2020.

Participants and study size, including dropouts

The survey targeted two groups of participants: HCPs prescribing/delivering SULIQUA pens (general practitioner [GP], endocrinologist/diabetologist, pharmacist, internist, and gastroenterologist) and patients/caregivers treated with SULIQUA (recruited by the participating HCPs) and followed up on diabetes by one or more of the following specialists (GP, endocrinologist/diabetologist, gastroenterologist, diabetes specialist nurse, other specialty).

The target number of completed surveys for the study was 384 for a precision level of 5% and assuming worst-case hypothesis of 50% proportion of correct answers. Assuming 85% HCPs would complete the questionnaire, it was estimated that a target of 450 HCPs would need to be surveyed.

Overall, among the 23969 targeted HCPs (from OneKey reference lists), 12566 (52.4%) HCPs could be contacted (i.e. reported receiving email or paper mail or answering the telephone call). Of them, 818 (6.5%) agreed to participate and 423 (3.4%) completed the questionnaire (all of them completed the Web questionnaire), a number higher than the target 384. Overall, cooperation rate of the HCPs (i.e. HCPs who completed questionnaire among those who agreed to participate) was 51.7%.

Of the HCPs completing the questionnaire, 67 (15.8%) also recruited patients. In total 442 patients/caregivers completed the questionnaire (a number higher than the target 384).

Variables and data sources

The surveys were conducted through a Web questionnaire translated into local language. The survey questionnaires comprised of multiple-choice and true/false questions. The HCP questionnaire was developed and tested among six HCPs for its understanding, consistency, and the appropriateness of medical terms. HCPs' comments were implemented in the final version. In addition, the patient/caregiver questionnaire was also tested among six non-HCPs for optimal readability by patients.

Data management, review, validation: Data Quality Control was conducted by IQVIA Primary Intelligence, a division of IQVIA specialising in telephone- and Web-based surveys. Collected data was entered and stored in country-specific databases. Data consistency checks were performed for removal of duplicates and identification of potential non-admissible values.

- **Variables and evaluation criteria:** The main evaluation criteria for the effectiveness of the aRMMs in HCPs and patients were the three following success factors: receiving the EMs, understanding EMs messages, and EMs implementation. Participation by HCPs was described by contact rate, response rate, cooperation rate and refusal rate. In addition, information was collected to describe the HCPs' characteristics and practice, and the patients' characteristics and which physician´s specialty are taking care of them.

Data Analysis: Statistical analysis was conducted using statistical analysis system (SAS®) software V9.4 on Windows™ (SAS Institute, North Carolina, US). Categorical variables were summarized as the number (n) and percentage (%) of subjects (HCPs and patients/caregivers) in each category. Percentages were displayed with one decimal place and were computed using the number of non-missing data as the denominator. In addition, a 95% confidence interval (CI) was also presented for percentages when relevant. For continuous variables, descriptive statistics included the number of non-missing observations (n), the mean and standard deviation (SD), median, first quartile and third quartile, minimum and maximum values (Min, Max). To account for the sampling design, the results of the HCP survey were weighted back according to the real proportion of HCPs from OneKey list. The results of the patients/caregiver's survey were weighted back based on sales volume of SULIQUA in each country.

The following individual definitions was considered for each success factor of the aRMMs effectiveness, for HCPs:

- Receiving EMs: Any HCP who received at least one of the following EMs (HCP guide, patients/caregivers guide or letter containing important information for HCPs and patient guide for patients/caregivers)
- Understanding EMs messages: Any HCP who provided ≥75% correct answers to knowledge questions, i.e. answered correctly ≥11 of the 14 questions assessing knowledge
- EMs Implementation: Any HCP who provided ≥75% correct answers to implementation questions, i.e. answered correctly ≥12 of the 15 questions assessing implementation

The following individual definitions was considered for each success factor of the aRMMs effectiveness, for patients/caregivers:

- Receiving EMs: Any patient/caregivers who received the patient guide
- Understanding EMs messages: Any patient/caregiver who provided ≥75% correct answers to knowledge questions, i.e. answered correctly ≥eight of the ten questions assessing knowledge
- EMs Implementation: Any patient/caregiver who provided ≥75% correct answers to implementation questions, i.e. answered correctly ≥six of the eight questions assessing implementation

Proportions of successful HCPs and Patients/caregivers for each of the three success factors (i.e. receiving EMs, understanding EMs, and EMs implementation) were calculated; the aRMMs were deemed as effective if at least 2 of the 3 pertaining proportions ≥80%.

Results

Among the 12566 HCPs contacted for wave 1 and 2, 818 (6.5%) agreed to participate and 423 completed the questionnaires, a number that is higher than the target 384. Cooperation rate of the HCPs (i.e. HCPs who completed questionnaire among those who agreed to participate) was 51.7%. Overall, 442 patients/caregivers completed the survey the survey having been recruited by 67 of the participating HCPs.

Description of Survey participants

Most of the participant HCPs were endocrinologists/diabetologists (61.9%, n=262), followed by GPs (29.3%, n=124) and internist (8.3%, n=35). The most common work setting for participating HCPs was offices (80.9%, n=342), followed by hospitals (22.1%, n=93) and diabetes care clinics (12.6%, n=53). The majority of HCPs (75.6%, n=320) had >10 years' experience treating diabetic patients. The median number of patients treated with/delivered SULIQUA in the previous three months were four patients. Some trends were observed within the countries' samples. In Czech Republic, Hungary and Romania there was a higher proportion of endocrinologists/diabetologists (83.7%, n=108; 78.4%, n=29 and 97.9%, n=95, respectively) whereas in Belgium and United Kingdom (UK) the majority of HCPs were GPs (72.7%, n=48 and 85.5%, n=71 respectively). Within the small number of HCPs in Slovenia, the majority were internists (63.6%, n=7). There were no GPs in Czech Republic and no internists in UK. Offices was the most common workplace in Czech Republic (57.4%, n=74), Slovenia (81.8%, n=9), Belgium (81.8%, n=54) and Romania (76.3%, n=74) whereas in Hungary majority of HCPs worked in diabetes care clinics (83.8%, n=31) and/or hospitals (64.9%, n=24) and in UK the same number of HCPs worked both in offices and diabetes care clinics (55.4%, n=46). The HCPs were more experienced in Czech Republic, Hungary, Slovenia, Belgium, and UK (>75% had more than 10 years of experience) than in Romania (slightly less than half with 10 years of experience).

The majority of the recruited patients/caregivers were aged 41-70 years old (86.7%, n=383) and there were slightly more females (51.6%, n=228). Patients/caregivers could be followed by one or

more HCPs. The vast majority were followed by endocrinologists/diabetologists (93.7%, n=414) 18.6% (n=82) was followed by GPs and 7.7% (n=34) by diabetes specialist nurse. The most frequently reported SULIQUA trainer was a diabetes care clinic (72.6%, n=321), and fewer were trained by a nurse (36.4%, n=161) or by a GP (11.3%, n=50). Most of the patients/caregivers had between 3 to 12 months of treatment with SULIQUA (57.7%, n=255) with 27.1% (n=120) having more than 12 months. Two-thirds were using SULIQUA (10-40) peach coloured pen. Some trends were observed within the countries' samples. Slovenia and Belgium had a higher proportion of patients/caregivers older than 60 years (61.9%, n=13 and 45.8%, n=11) whereas UK registered the higher proportion of younger patients/caregivers with 83.9% (n=26) aged between 30 and 60 years old. The vast majority of patients/caregivers were seen by endocrinologists/diabetologists in Czech Republic (98.7%, n=155), Hungary (98.5%, n=66), Belgium (98.5%, n=23), Slovenia (100%, n=21) and Romania (100%, n=142) and by GPs in the UK (64.5%, n=20). In Hungary and Belgium patients/caregivers were also frequently seen by GPs (47.8%, n=32 and 58.3%, n=14). More than 75% of the patients/caregivers in all countries reported they were trained on SULIQUA by a nurse and/or diabetes care clinic in all countries except Belgium where endocrinologists/diabetologists trained 29.2% (n=7) of the patients/caregivers. The majority of patients/caregivers in the UK and Slovenia had less than six months experience with SULIQUA (90.0%, n=28 and 61.9%, n=13, respectively with less than six months experience) whereas the majority in other countries had more experience. Most of the patients/caregivers were using the SULIQUA (10-40) peach coloured pen in all countries except Czech Republic where a similar number were using each pen.

Effectiveness of aRMMs

Overall, the aRMMs were not successful in HCPs, as none of the three success factors were obtained by more than 80% of HCPs: 'receiving the EMs' was met by 70.4% of the HCPs, 'understanding EMs messages' by 40.8% of HCPs and 'EMs implementation' by 12.4% of HCP. Although the results per specialty and country are not generalisable, the trends observed in the sample suggested that aRMMs were not successful by HCP specialty.

The proportion of the overall HCPs who had at least one, two and all three success factors were 78.0% (n=330), 39.4% (n=167) and 6.2% (n=26), respectively. Removing the success factor components that depended on reviewing the checklist and providing the patient guide to patients, resulted in considerable increase on the success factor 'EMs implementation', from 12.4% (n=52) to 45.9% (n=194). In addition, the analysis of 'EMs implementation' success factor by number of patients prescribed SULIQUA in the three months prior the survey, showed an increase of success with an increased number of patients prescribed SULIQUA: 10.4% (n=14) of HCPs who prescribed to ≤4 patients, 19.8% (n=19) of those who prescribed to 5-8 patients, 27.5% (n=19) of those who prescribed to 9-12 patients and 29.3% (n=36) of those who prescribed to more than 12 patients.

When considering the HCP specialty trends in the sample, endocrinologists/diabetologists and internists met the 'receiving the EMs' success factor (93.1%, n=244 and 88.6%, n=31) but not GPs (72.6%, n=90). The 'understanding EMs messages' success factor was met by a higher proportion of endocrinologists/diabetologists and internists than of GPs (66.0%, and 60.0%, vs. 35.5% respectively) while the 'EMs implementation' success factor was met by a higher proportion of GPs and endocrinologists/diabetologists than internists (19.4% and 23.2%vs. 8.6%).

When considering the country trends in the HCP sample and albeit not generalisable to the country populations, all countries were successful at 'receiving the EMs' (>80%) except Belgium where only 62.1% (n=41) met the success factor. Only Slovenia met another success criterion ('understanding EMs messages' by 81.8%, n=9) but there were only 11 participating HCPs in the country. Romania also nearly met the criteria with 78.4% (n=76) 'understanding EMs messages. Belgium presented the lowest results in the three success factors: 62.1% in the 'receiving the EMs', 39.4% in the 'understanding the EMs messages' and 4.5% in the 'EMs implementation'.

This study also aimed to assess HCPs awareness about the importance of medication errors. The vast majority, 77.5% (n=328) of HCPs knew that medication errors were the most common cause of adverse events and patients should ask, if needed, clarifications on how to use their pen and on how many dose steps they require. In addition, 84.3% (n=357) of HCPs reported they would educate their patients to report side effects/medication errors to their doctor or pharmacist.

The aRMMs met the effectiveness criteria for patients/caregivers as two success factors were reached by >80.0%: 'receiving EMs' (87.3%, n=386) and 'understanding EMs messages' (83.5%, n=369). Slightly less than a third (29.6%, n=131) answered correctly the questions assessing 'EMs implementation'. The proportion of the patients/caregivers who had at least one, at least two and all three appropriate responses to the three success factors were 97.1% (n=429), 76.2% (n=337) and 27.1% (n=120), respectively.
When considering the specialty trends in the patients/caregivers sample, the aRMMs was successful in patients/caregivers followed by endocrinologists/diabetologists, as ≥80% were successful in 'EMs receiving' and 'Understanding EMs messages'. Patients/caregivers followed by diabetes specialist nurse or GPs also nearly met the criteria (≥80% successful in the 'Receiving the EMs' and ≥70% successful in the 'Understanding EMs messages'). Patients/caregivers followed by diabetes specialist nurses presented with higher 'EMs implementation' success factor results than those followed by GPs or endocrinologists/diabetologists (44.1% vs. 25.6% and 25.6%, respectively).

When considering the country trends in the patients/caregivers' sample and albeit not generalisable to the country populations, the results suggest the aRMMs for patients/caregivers were effective in Czech Republic, Slovenia, and Romania but not in Belgium, Hungary, and UK. Belgium presented with the lowest results: only 37.5% (n=9) patients/caregivers received the guide, 54.2% (n=13) understood EMs messages and none met implementation success factor. In the UK, 96.8% (n=30) patients/caregivers received the guide, 61.3% (n=19) understood EMs messages and 29.0% (n=9) met 'EMs implementation' success factor. In Hungary, 98.5% (n=66) received the guide, 77.6% (n=52) understood EMs messages but 26.9% (n=18) met implementation success factor.

Success Factor: Receiving EMs

Among HCPs, the guide for HCPs (57.8%, n=245) was the most commonly received material, followed by the letter containing important prescribing information (46.3%, n=196) and the guide for patients/caregivers (39.6%, n=168).

When considering the HCP specialty trends in the sample, more endocrinologists/diabetologists and internists received the guide for HCPs (85.5%, n=224 and 77.1%, n=27, respectively) and the letter (68.3%, n=179 and 62.9%, n=22, respectively) than GPs (60.5%, n=75 received the guide

and 46.0%, n=57 received the letter). Receipt of the patient guide was most frequently reported among endocrinologists/diabetologists (71.8%, n=188) than other specialties (51.4%, n=18 internists and 37.1%, n=46 GPs). When considering the country tends in the HCP sample, the guide for HCPs was received by a vast majority (≥75%) of HCPs in all countries except Belgium where approximately half received it (48.5%, n=32). The patient guide was received by 84-87% of the HCPs in Hungary (n=32) and Romania (n=81), by 72.7% (n=8) of those in Slovenia, by 51-54% of those in UK (n=42) and Czech Republic (n=69) and by 31.8% (n=21) of those in Belgium. Between 70-74% of the HCPs in Czech Republic (n=94), Slovenia (n=8), and Romania (n=72) received the letter whereas 40-50%% of those in Hungary (n=18), UK (n=41) and Belgium (n=27) received it.

Regarding the receipt of EMs criteria among patients/caregivers, the vast majority of them reported having received (87.3%, n=386) SULIQUA patient guide.

No trends were observed across participants followed by different specialties in the patients/caregivers' sample. When considering the country trends in the patients/caregivers sample, >80% received the patients guides in all countries except Belgium where only 37.5% (n=9) received it.

Success Factor: Understanding EMs messages

The vast majority (≥75%) of the HCPs answered correctly two of the five dose titration questions, four of the five pen choice questions and all safety messages. More specifically, when considering dose titration questions, the vast majority (≥75% HCPs) knew that "doses >40 steps/day titration must be continued with the 30-60 pen" and that "SULIQUA must not be used for daily doses >60 steps". A lower proportion of HCPs correctly identified the false statements, i.e. "Patients who received between 20 and 30 units of insulin, should start with 30 dose steps daily" (56.9% correct answers) and "Patients who received insulin or insulin glargine twice a day, should have a reduction of total daily dose of SULIQUA by 10%" (46.5% correct answers). When considering pen choice questions, the vast majority (≥75% HCPs) knew the daily dose steps that each SULIQUA pen allows, that both pens contained insulin glargine in a strength of 100 Units/mL and that patient cannot use the colour of pen of his choice. Lastly, when considering safety messages the vast majority (≥75% HCPs) answered correctly all statements (i.e. patients may experience side effects and should talk to their doctors and pharmacists, medication errors are the most common cause of adverse events and patients should ask clarifications on how to use the pen and how many dose steps, patients may experience dysglycemia and should measure their blood sugar more frequently after shift to SULIQUA and that the patients do not need to be monitored for bone pain and swelling). When considering the HCP specialty trends in the sample, the vast majority (≥75%) of the endocrinologists/diabetologists and internists answered more correctly to dose titration and pen choice questions (four of five dose titration and all five pen choice) than GPs (two and four correct answers, respectively). Regarding safety messages, a lower extent of endocrinologists/diabetologists (70.2%, n=184) knew that "medication errors are the most common cause of adverse events and patients should ask, if needed, clarifications on how to use their pen and on how many dose steps they require" than GPs (79.8%, n=99) or internists (82.9%, n=29). When considering the country trends in the HCPs sample, the vast majority (≥75%) of the HCPs in Czech Republic, Slovenia, and Romania correctly answered a higher number of dose titration questions (four of five) than those in Hungary (three of five), UK (two of five questions),

and Belgium (one of the five). Regarding pen choice questions, the vast majority (≥75%) of the HCPs in Czech Republic, Hungary, Slovenia, Romania, and UK answered correctly all five questions whereas in Belgium >75% HCPs answered correctly four of the five questions. Conversely, the vast majority (≥75%) of the HCPs in Belgium answered correctly all four safety messages questions, a higher number than those in Czech Republic, Hungary, Slovenia, and UK (three of four) and in Romania (two of four with another one at 74%).

Eighty percent or more of the patients/caregivers answered correctly nine of the ten questions about understanding EMs messages, namely, that dose pointer shows number of dose steps to be injected; one dose step of SULIQUA contains one unit of insulin glargine 100U/ml plus a corresponding amount of lixisenatide; the pen should not be used by another person even when needle is changed; a syringe cannot be used to withdraw SULIQUA from a pre-filled pen; it is important to closely monitor blood sugar level; the prescription should mention which pre-filled pen to be used; that SULIQUA [10-40] and [30-60] pens allow a daily injection of doses between 10-40 and 30-60 dose steps, respectively; and, that if the total daily dose is more than 60 dose steps, then none of the SULIQUA pens should be used. A slightly lower proportion of patients/caregivers (71.9%, n=318) identified the statement “one dose step of SULIQUA only states the amount of lixisenatide” as false. When considering the HCPs specialties trends in the patients/caregivers’ sample, the results were consistent across specialties who followed the patients/caregivers: the vast majority (≥75%) correctly responded to all questions, except the one related to the amount of lixisenatide per dose step of SULIQUA where a lower proportion of patients/caregivers followed by GPs answered correctly (51.2%, n=42) than those followed by endocrinologists/diabetologists (67.9%, n=281) or diabetes specialist nurse (79.4%, n=27). When considering the country trends in the patients/caregivers’ sample, the vast majority (≥75%) of those in Romania answered correctly all ten questions about understanding of EMs messages. A lower proportion of patients/caregivers in Hungary, Slovenia and UK identified the statement “one dose step of SULIQUA only states the among of lixisenatide” as false (3.0%, n=2; 38.1%, n=8; 58.1%, n=18, respectively). In Belgium and UK, a slightly lower proportion of patients/caregivers knew that none of the SULIQUA pens should be used if the total daily dose is more than 60 dose steps (74.2%, n=49 and 72.3%, n=60) compared with other countries (≥82%).

Success Factor: EMs Implementation

More than 90% of the HCPs who reported receiving the HCP guides, indicated that they frequently (58.9% (n=144) or occasionally (37.1%, n=91) used it when prescribing/dispensing SULIQUA and also when changing SULIQUA pen strengths (42.4%, n=104 and 49.3%, n=120, respectively). The vast majority also frequently (34.6%, n=85) or occasionally (56.0%, n=137) reviewed each point of the checklist. Also, > 90% of the HCPs who reported receiving the patients´ guide, indicated that they frequently (61.1%, n=103) or occasionally (34.1%, n=57) provided guides to patients/caregivers prior to initiating SULIQUA. The vast majority (≥75%) of HCPs answered correctly four of the seven questions related to communication/messages to be provided to the patients. More specifically, they considered that the following messages should be provided to patients: “patients should report any side effect/medication error to their doctors or pharmacists”, “the patients should closely monitor their blood sugar level when starting SULIQUA”, “the patients should read the patient guide, information leaflet and the leaflet in SULIQUA packaging” and that patients should not use the same needle for several injections. Only 37.8% (n=160) of HCPs considered they should communicate to the patients that “the peach

colour pen and the olive colour pen contain the same concentration of insulin". Concerning which information is important to be indicated in the prescription for SULIQUA, 77-82% selected the number of dose steps, the strength of SULIQUA and the name of the product. A lower proportion of HCPs (48.5%, n=205) considered that the associated dose range/strength should also be included in the prescription.

When considering the HCP specialty trends in the sample, GPs used the guide more frequently than endocrinologists/diabetologists or internists when prescribing/dispensing SULIQUA (69.3%, n=52; 47.8% , n=107 and 40.7%, n=11, respectively), when changing SULIQUA strength (53.3%, n=40; 37.9%, n=85 and 29.6%, n=8, respectively). GPs also reviewed each point of the checklist more frequently than endocrinologists/diabetologists or internists (48.0%, n=36; 21.9%, n=49 and 22.2%, n=6, respectively). Almost two-thirds of endocrinologists/diabetologists and GPs frequently provided guides to patients/caregivers prior to initiating SULIQUA (64.4%, n=121 and 63.0%, n=29, respectively) whereas over one-third of internists did the same (38.9%, n=7). The vast majority (≥75%) of HCPs correctly selected most messages to be provided to patients, with five of seven messages for endocrinologists/diabetologists and internists, and four of seven for GPs. When considering the country trends in the HCP sample, more HCPs in Hungary, UK, Belgium, and Romania (56-66%) used the HCP guide frequently when prescribing or dispensing SULIQUA than those in Czech Republic (36.0%, n=36). Using the guide when changing SULIQUA pen strengths was more frequent in UK, Hungary, and Romania (50-60%) than in Czech Republic and Belgium (23-34%). Also, a higher proportion of HCPs in Hungary and UK reviewed each point of the checklists frequently (45-48%) than those in Czech Republic, Belgium, and Romania (11-34%). The vast majority (≥75%) of HCPs correctly selected most messages to be provided to patients, with six of seven messages in Slovenia and UK, five of seven messages in Romania, four of seven messages in Czech Republic and Hungary, two of seven messages in Belgium. The vast majority (≥75%) of HCPs in UK selected all the four information types that should be indicated in the prescription whereas in the other countries only between 40-60% would indicate the "associated dose range/strength". In Romania, 95.9 % (n=93) would include the number of dose steps to be injected but a lower proportion (57-67%) would include any of the other information.

Among the 386 patients/caregivers who received the SULIQUA patient guide, 93.5% (n=361) reported reading it. When facing any difficulty in understanding the prescription or use of SULIQUA pen, the vast majority of patients/caregivers (92.1%, n=407) would ask a physician. This is followed by reading the information leaflet from the SULIQUA package (50.5%, n=223), reading the SULIQUA patient guide (47.5%, n=210) and asking a nurse (40.0%, n=177). When considering the specialties trends in the patients/caregivers sample, a lower proportion of those followed by diabetes specialist nurse read the patients information leaflet than those followed by GPs or endocrinologists/diabetologists (73.5%, n=25; 86.6%, n=71 and 83.6%, n=346 respectively). The proportion of patients/caregivers who reported reading the SULIQUA patient guide if they faced any difficulty in understanding the prescription or use of SULIQUA pen was higher among those followed by the diabetes specialist nurse (52.9%, n=18) than among those followed by endocrinologists/diabetologists (40.3%, n=167) or GPs (37.8%, n=31).

When considering the country trends in the patients/caregivers sample, the vast majority ≥75%) of those in all countries read the Patient Information Leaflet except in Belgium where half of them read it. The proportion of patients/caregivers who reported reading the SULIQUA patient guide if

they faced any difficulty in understanding the prescription or use of SULIQUA pen was higher in Romania (63.4%, n=90) followed by 46.3% (n=31) in Hungary, 41.9% (n=13) in UK, 33.3% (n=7) in Slovenia, 22.9% (n=36 in Czech Republic) and none in Belgium.

Discussion

This report provides important insights about receiving, understanding and implementing in the safety messages conveyed by the HCPs' and patients' guides for SULIQUA pre-filled pen, a fixed-ratio combination of insulin glargine and lixisenatide. The results suggest that aRMMs were effective (i.e. ≥80% successful in two success factors: 'receiving the EMs' and 'understanding EMs messages') for patients/caregivers, despite not meeting 'EM implementation' success factor. On the contrary, the aRMMs defined effectiveness criteria were not met for HCPs. None of the HCP success factors met the 80% success threshold. Given that the patients/caregivers are the ultimate users of the product, the fact that they read and understood the EMs key messages is reassuring. The stringent definition used for 'EMs implementation' criteria among patients/caregivers (i.e. requiring the selection of all sources of information [physicans, and pharmacists, and patient guide and internet, etc.] for clarifying questions) may have contributed to the low 'EMs implementation' success factor results (29%) in patients/caregivers when considering they presented solid understanding of the EMs messages.

When considering the individual success factors for HCPs, 'receiving the EMs' was nearly achieved (70.4%). This result is mostly driven by the countries that weighted more in the overall result, in this case Belgium, which was the only country where receipt of EMs was lower than 80.0%, more precisely, 62.1%. Overall, 'understanding EMs messages' was only met by 40.8% of the HCPs. The definition of this criteria considered additional messages than those targeted to be included in the aRMMs as per RMP, namely questions related with dose titration. The results were reassuring about HCPs knowledge of safety messages and pen choice which were the key messages covered in the aRMMs (>70% HCPs answered each correctly). The success factor 'EMs implementation' was only met by 12.4% HCPs with a considerable increase to 45.9% when disregarding components that depended on having received the materials, which suggests that those HCPs who received the materials were better at communicating key messages to patients and including key information in the prescription. Also of note, the higher the number of patients/caregivers treated with SULIQUA in the previous three months, the higher the success rate for 'EMs implementation' (from 10.4% among HCPs who treated ≤4 patients/caregivers to 29.3% among those who treated >12 patients) which reflects the fact that HCPs seeing more patients/caregivers are more used to communicate the key EMs messages. This suggests that the low results observed for 'EMs implementation' success factor could be also attributed to the slowly progressive uptake of SULIQUA. Despite the overall low results for the 'EMs implementation', the results were reassuring that HCPs communicated to patients' messages related to safety topics. Indeed, the vast majority of HCPs (≥75%) explained to their patients about the need to change needle for each injection, to monitor blood sugar level when starting SULIQUA, reading the patient guide, information leaflet and package leaflet and reporting any side effect/medication to their doctor or pharmacist. A lower proportion would communicate that blinded patients should be helped which may have been influenced by whether they had patients in those circumstances, and a minority would be communicating that both pre-filled pens contain insulin glargine in a strength of 100 units/ml despite knowing this is true as 86% answered the corresponding knowledge question correctly. It is possible that HCPs did not consider this

information important or even relevant for the patients/caregivers given they would be prescribed one of the pens. The vast majority of HCPs (>75%) knew that the prescription should indicate the number of steps to be injected, the strength of pen and name of product but only around half would also indicate the associated dose range/strength, possibly because they had already selected dose steps and strength. Lastly, it has to be noted that EMs were distributed more than 2 years prior to the survey conduction; it may explain part of the non-effectiveness of aRMMs in HCPs measured by the survey.

When considering the individual success factors for patients/caregivers, 'receiving EMs' and 'understanding EMs messages' were successfully met overall. Although the study was not designed to assess results at the country level and thus they cannot be generalised, the participants in all countries were successful for the 'receiving the EMs' criteria except Belgium, where only 38% of the 24 participants reported receiving the patient guide which is possibly due to the fact that the majority of HCPs in this country have not received it and thus not distributed the materials. The participants in Hungary, Belgium and UK did not meet the 80.0% threshold for the 'understanding EMs messages' success factor. However, no specific trends in terms of messages less well understood in these countries were observed as compared to other countries. The 'EMs implementation' success factor was met only by 29% of patients/caregivers'. However, this success factor is likely underestimated due to strict definition of success used for this criterion requiring that patients/caregivers would select six out of eight sources of information about SULIQUA. In particular, it is unlikely that patients/caregivers would respond to the question 'which source of information to use in case of difficulties', by selecting several different sources (physician, nurse, pharmacist, patient guide, information leaflet, web) and the definition used in this criteria required them to select at least four. Of note, 94% of the patients/caregivers reported reading the patient guide but when faced with challenges understanding the prescription or SULIQUA use they were more likely to ask a physician (92%) than reading the patient leaflet or guide (50%). The results from the HCPs survey, showed that for HCPs, the physician would also be the most relevant source of information on appropriate use of SULIQUA (80.2%) which emphasises the importance of ensuring HCPs are well aware of SULIQUA guidance. In addition, approximately one-third of patient/caregivers reported having been trained by a nurse indicating they should also be targeted by education materials. Notwithstanding, patient/caregivers demonstrated appropriate levels of reading the EMs and knowledge which indicates the initial training and information read in the EMs was effective.

This study had a number of strengths: the use of a large worldwide database for the identification of HCPs, the use of randomised stratified sampling to ensure adequate strata representation criteria, multiple attempts to contact participants and the weighting method according to the real proportion of HCPs from OneKey lists. As with any other survey, the potential for selection bias is an inherent bias/limitation to any study based on volunteer participation. To quantify this, the distribution of the stratification criterion of HCPs was compared between participants and non-participants and the two datasets were comparable suggesting that the impact of selection bias, even if present, was limited. Cluster sampling bias for patients/caregivers cannot be excluded as selection of patients dependent on the participation of certain HCPs and their patient pool. This may have resulted in some overestimation of the success factors and effectiveness of aRMMs among patients. Nevertheless, the invitation to participate was distributed randomly to patients and the answers were collected directly from the patient/caregivers anonymously without HCPs acting as intermediates which increases the validity of their results. Despite some of these

limitations, while this survey may not be representative of the entire population of SULIQUA users, the findings are derived from a large population of HCPs and patients/caregivers and provide valuable insights about effectiveness of aRMMs.

In conclusion, the results suggest that aRMMs for patients/caregivers were effective but those for HCPs were not effective as per study criteria. However, it should be reminded that the patients are the ultimate users of the product and therefore the results are reassuring on the way patients were informed by their HCPs. The effectiveness of the aRMMs tended to be higher among endocrinologist/diabetologists and lower among GPs overall and HCPs in Belgium.