OPEN

Patient Preferences for Rituximab Additional Risk Minimization Measures: Results From an International Online Survey

Kristyna Schneiderova, PhamD, PhD, Nathalie Bere, MSc,**
Doris Irene Stenver, MD, MPA,† and Sabine M. J. M. Straus, MD, PhD, MSc*‡*

Objective: Patients' opinions are essential in optimizing risk minimization measures (RMMs) because they bring their real-life experience of disease management and medicines' use into the regulatory assessments. The aim of the survey launched in 2018 by the European Medicines Agency, in collaboration with the Pharmacovigilance Risk Assessment Committee, was to consult targeted patient groups treated with rituximab for nononcology indications to evaluate their preferences on how to receive information on progressive multifocal leukoencephalopathy and (serious) infections. Additional RMMs such as educational materials for physicians and patients including a patient alert card (PAC) and a patient brochure (PB) are in place to minimize these risks.
Methods: A question-based online survey in English created on the EU-Survey platform and disseminated primarily via relevant European patient organizations.
Results: Most patients (47 of 61) had knowledge of these potential adverse effects. Mostly, they were informed by a healthcare professional. Both a PAC and a PB were supported as useful tools to raise awareness of these adverse effects and thus minimize the potential risks among patients. Where the participants had to choose only 1 of these educational materials, 43 of them preferred a PAC, a shorted description that is always held by the patient and reaches the relevant healthcare professional when needed.
Conclusions: Collecting patients' preferences supports periodic assessment of additional RMMs and increase transparency of regulatory processes. Considering the limitations of this initial survey, further investigation is needed to generalize the results into patients' safety outcomes.

Key Words: patient, preference, rituximab, educational material, patient alert card, risk minimization measures, drug safety, effectiveness

(*J Patient Saf* 2022;18: 331–336)

An integral tool that facilitates identification, characterization, monitoring, and minimization of risks of medicinal products is the Risk Management Plan (RMP). The EU-RMP is a dynamic document that should be updated throughout the life cycle of the product and consists of 3 key components: the safety specification, the pharmacovigilance plan, and the risk minimization plan. The risk minimization plan describes the measures to minimize the risks. Some serious risks may not be sufficiently minimized by routine measures (i.e., the product information) and may need additional risk minimization measures (RMMs) to ensure that the benefits of these products continuingly outweigh their risks.[1–3] From 2006 to 2015, additional RMMs have been imposed on approximately one quarter of all EU centrally authorized medicines, mostly involving blood products, antineoplastic, and immunomodulating agents. All additional RMMs required the provision of educational materials, most frequently targeting healthcare professionals (HCPs) and secondly patients.[4,5]

Because of the complexity, many of the risks associated with the use of a medicine will only be fully characterized after authorization.[1] In the rituximab example, its mechanism of action means that patients have an increased risk of (serious) infections, including progressive multifocal leukoencephalopathy (PML), a very rare but progressive, demyelinating disease of the central nervous system that can lead to death or severe disability.[6,7]

As patients can bring their real-life experience of diseases, as well as on disease management, their input in proactive benefit-risk medicinal product life cycle management is essential. Based on recent data, the inclusion of patient preferences is a topic of growing interest. It is pivotal in outcome research as it can help understand patients' values of certain treatment outcomes, benefit-risk trade-offs, and preference heterogeneity, and it also supports transparency and trust in regulatory processes.[8–10] However, they are only a few practical examples that have been published for wider discussion.[11] The European Medicines Agency (EMA) has been actively engaging with patients since its creation; patients are voting members in some of its scientific committees, including the Pharmacovigilance Risk Assessment Committee (PRAC).[12] The agency has continuously refined and expanded its methods to ensure that there are opportunities to include patients at all stages along the regulatory lifecycle, e.g., through pilot testing of various engagement methodologies, in collaboration with EMA's network of patient organizations.[9] Important examples of active engagement are public hearings, stakeholder meetings, and written consultations, all of which can engage either broader or targeted patient groups to understand and evaluate their preferences on proposed RMMs to optimize uptake of the assessment outcomes.[13] Similarly, U.S. Food and Drug Administration has been systematically engaged in dialog with the wider stakeholder community for several years to incorporate the relevant patient experience data into the structured benefit-risk assessment, e.g., in panels or public workshops. Each meeting resulted in a Voice of the Patient report that can further inform regulatory decision making.[14] With the passage of the 21st Century Cures Act, the Food and Drug Administration also began developing a series of 4 methodological patient-focused drug development guidance documents.[15]

Several additional RMMs to address the risks initially identified in the rheumatoid arthritis (RA) indication were recommended by the PRAC as a condition for the safe and effective use of the product due to the risk of John Cunningham virus infection with resultant PML and death in a rituximab-treated RA patient. These consisted of a direct healthcare professional communication distributed in November 2008 and a patient alert card (PAC)

From the *European Medicines Agency, Amsterdam, the Netherlands; †Danish Medicines Agency, Copenhagen, Denmark; and ‡College ter Beoordeling van Geneesmiddelen–Medicines Evaluation Board, Utrecht, the Netherlands.
Correspondence: Kristyna Schneiderova, PhamD, PhD, State Institute for Drug Control (SUKL), Srobarova 48, 100 41 Praha 10, Czech Republic (e-mail: kris.schneiderova@gmail.com).
The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or of the European Medicines Agency or one of its committees or working parties with which the authors are affiliated. As of October 2019, K.S. is a full-time employee of State Institute for Drug Control, Czech Republic; and as of March 2019, D.I.S. is an independent pharmacovigilance advisor at Unique Advice. However, all of their contributions to this work were made before their respective time of departure, as part of their employment at the European Medicines Agency and Danish Medicines Board, respectively. The other authors disclose no conflict of interest.

distributed since May 2009.[16–18] Further educational materials for patients (patient brochure [PB]) and physicians (physician brochure) were subsequently implemented for all nononcology indications in 2012 to increase awareness about this risk.[18] Key elements are outlined in Annex IIB of the product information.[6,7,19–23]

The aim of the PAC is to inform patients of the need for vigilance with respect to general infections and PML in particular so that they seek medical attention early. The rationale was that with a timely diagnosis of infections and/or PML, treatment with rituximab could be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy considered. Ability to carry the PAC with ease is a key design feature of this tool.[1] The PAC is supplied within rituximab drug cartons attached to the package leaflet and additionally can be distributed via HCPs depending on national legal requirements.[6,7,24] In addition to the PAC, more detailed information about important early symptoms and other aspects related to infections and PML is provided in a PB, which should be given to patients by their HCPs depending also on national legal requirements. The educational materials for physicians are to help them communicate key safety messages to patients and to increase their awareness of the need for timely and appropriate measures to diagnose PML.[25]

As the need to continue additional RMMs may change over time, the periodic evaluation of their effectiveness throughout the lifetime of a medicine is a legal obligation and a crucial aspect of continuous pharmacovigilance to establish whether an intervention has been effective or not and whether any improvements are needed.[1–3] Currently, there is still limited knowledge on the use of evaluation tools, as well as the determinants of RMMs success. Studies should use a "dual evidence" approach as recommended by the guidelines and literature to assess both process and outcome indicators.[26] However, most evaluations have so far concentrated on process measurements, such as tool distribution and utilization results, rather than clinical outcomes.[27] Behavior and knowledge were the most often assessed process indicators. Outcome indicators included occurrence of adverse reactions, pregnancy, off-label use, and medication errors. None of the latter used a pre-post design, comparing the frequency of the adverse outcome before and after the implementation of RMMs.[26] Generally, studies evaluating the results of cross-sectional surveys assessing the effectiveness of RMMs in Europe between 2011 and 2018 showed that educational materials were received by 50% to 80% of patients and read by more than 90%. Patients only scored knowledge more than 60% in 38% of items.[28]

In monitoring the outcome of RMMs, the EMA can support PRACs scientific assessment through the integration of data provided by member state resources and research activities.[1] Based on regulatory assessment, further action was requested in 59% of cross-sectional studies, which included distribution strategies, redistribution, and follow-up assessment, changes to existing materials, further data awaited, and, in a minority, removal of the materials.[28] As effective educational tools can improve patient safety,[1] the aim of this research was to obtain a better understanding of patients' preferences regarding additional RMMs to ensure that the proposed materials were "patient relevant" and would realistically support risk minimization when implemented. To achieve this, a survey was launched by the agency, upon request of the PRAC among the targeted patient groups currently treated with rituximab for nononcology indications.

METHODS

Design

An online questionnaire to gather patients' risk awareness and preferences on educational materials was designed in English in accordance with the Guideline on Pharmacovigilance Practises XVI Appendix 1 recommendation[1] and agreed by the PRAC.[29] There was a mix of both yes/no and open-ended questions (Table 1). The questionnaire also contained background information with examples of educational materials for patients (a PAC, a PB). The agreed survey was created using EU Survey, the European Commission's official survey management tool for creating and publishing forms available to the public. It was disseminated mainly not only via relevant EU patient organizations but also via EMA Twitter and LinkedIn channels to increase outreach.[25] The respondents were anonymous as the only personal information asked was their country of residence. Sociodemographic data were not collected.

Participants

Adult patients currently being treated with rituximab for nononcology indications authorized in the EU at the time of survey distribution as severe active RA, severe active granulomatosis with polyangiitis (Wegener's, GPA), and microscopic polyangiitis (MPA) who were voluntarily able to respond to the questions in English. Participants did not receive any remuneration.

Data Collection

Data collection took place between December 7, 2018, and January 22, 2019.

Data Analysis

All responses were analyzed individually in a digital tool Microsoft Excel 97-2004 Workbook by 2 of the authors using descriptive statistics, such as the percentage of participants responding, stratification by selected variable, or data on no response or incomplete response.

RESULTS

Sample Characteristics

A total of 61 participants completed the survey. One participant was excluded as he/she was treated for an oncology indication. Thus, a total of 60 participants were included in the final sample (81.7% respondents were from EU countries, 18.3% from non-EU countries). Basic demographic information for the participants

TABLE 1. List of Questions

Q1: "Are you aware of the potential side effects in relation to infections and PML when taking rituximab?" (yes/no)

Q2: "If yes, where, or how did you learn about these potential side effects?"

Q3: "In addition to the leaflet, do you think that a Patient Alert Card (example attached) is useful to highlight the potential signs of infection and PML? Why? (please provide as much detail as possible)"

Q4: "In addition to the leaflet, do you think that a patient brochure (example attached), is useful to highlight the potential signs of infection and PML? Why? (please provide as much detail as possible)"

Q5: "If you had to choose only one of these additional educational materials which one would you choose?"

a. A patient alert card, a small document to be carried with you at all times

b. A patient brochure, providing you with additional details and kept at home.

TABLE 2. Participants Country of Residence

Country of Residence	No. Participants
European Union	
Croatia	1
Estonia	1
Finland	3
Ireland	6
Netherlands	1
Sweden	1
United Kingdom	36
Total	49
Non-EU	
Canada	1
United States	10
Total	11

is given in Table 2. Duration and type of rituximab treatment are summarized in Figure 1. The treatment period differed from 1 week to 16 years, and most patients were treated for GPA (41.7%), then for RA (21.7%), off-label indications (11.7%), and MPA (10%), and 15% did not specify the indication.

Patients' Awareness About Potential Adverse Effects in Relation to Infection and PML When Taking Rituximab

Forty-seven patients (78.3%) were aware of the potential adverse effects in relation to infection and PML compared with 13 patients (21.7%) who were not aware. Summary of sources is presented in Table 3 (more answers possible). Most patients were informed by HCPs. Second, the patients specified that they received written materials to be read (named as "information to read," "print," "letter," "leaflet," booklet," "information/patient leaflet," "drug information sheet," "literature," "participant information sheet"). The third source about adverse effects was Internet searches. The minority of patients learned about potential adverse drug reactions from available RMMs. In 1 case, information was shared from other patients.

Patients' Perspective on Rituximab Patient Alert Card

The majority of participants (57 in total, 95%) found a PAC a useful tool to highlight the potential signs of infection and PML. The main reasons cited were that a PAC is written in concise language, could catch the early symptoms, and make treatment more effective. It is also easily carried in a wallet and accessible for carers and other HCPs, e.g., in case of traveling abroad, emergency, or unconsciousness.

It was also suggested to make it using plastic material, or as a fridge or medicine cupboard magnet, to include the generic name instead of the brand name and include more information about immunosuppression as patients could be concomitantly treated with steroids. It could be given with each infusion as it could be lost in the meantime. In addition to a PAC, 1 patient suggested to have the option for genetic testing available before rituximab treatment initialization.

Three participants (5%) disagreed stating that the alert signs seemed rather vague to them, which most people would not see a PAC or they could lose it or generally not carry a paper card. Some participants also proposed to integrate a PAC into a digital format or health mobile phone application. When the participants had to choose only 1 of the available rituximab educational materials, 43 (71.7%) preferred PAC, a small document to be carried with them at all times.

Patients' Perspective on Rituximab PB

Most patients (56 in total, 93.3%) were of the view that a PB is useful to highlight the potential signs of infection and PML mainly if it is provided at the beginning of treatment. Patients acknowledged that a PB included more detailed information than a PAC and that it is informative and clearly written in lay language. It could be kept as a reference for them, family members, other HCPs (e.g., general practitioners, surgeries), and/or carers as well. They also proposed that a PB could be available online, updated regularly, and accessible in digital format, such as a mobile phone application, video, or audio for disabled patients as a printed brochure could be lost.

Only 3 patients (5%) felt that a PB is not useful to highlight the potential signs of infections and PML, e.g., the need of a concise summary was suggested as too much information can be scary or overwhelming and may be ignored. When receiving extensive information, it may be put into in a folder or thrown away. From that point, only 1 piece of easily accessible short wallet size information displayed in an interesting way or a package leaflet could be sufficient to inform them about the potential risks. One patient did not respond this question.

In case the participants had to choose only 1 of available rituximab educational materials, 17 participants (28.3%) preferred a PB, providing them with additional details and kept at home.

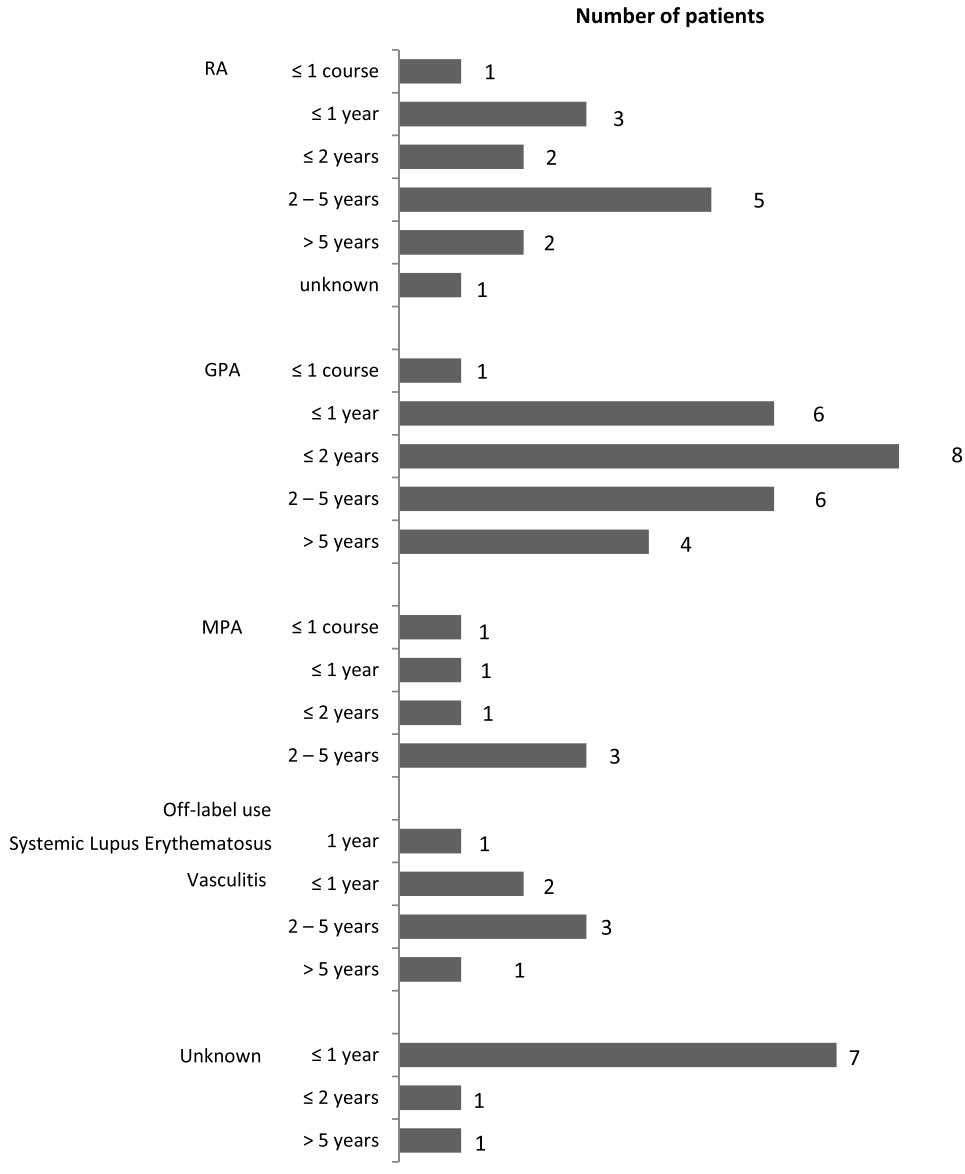
DISCUSSION

Summary of Main Findings and Interpretation

This survey should be seen as an opportunity to learn more about the collection and use of patients' preferences regarding proposed educational materials and understanding awareness of risks as well as additional practical suggestions for improvements. In general, familiarity with educational materials among patients and consumers through Europe is low.[9] More patient-friendly educational materials could help them be not only "aware" of risks but also understand the precise implications for their lives using shared decision making. Recent studies that examined patient preferences for RA treatment in several populations showed that most participants were willing to accept certain risks of adverse effects to gain potential benefits.[30]

Most patients were aware of the potential of rituximab related adverse effects of infection and PML with their main source of information being HCPs. This finding is in accordance with the results of a recent consultation with European patients and consumer organizations, which showed HCPs were considered the most trusted source of information.[9,31,32] Face-to-face physician-patient partnerships are essential for receiving information and when choosing among various therapeutic options to maximize adherence.[9,33]

Although the patients stated that both a PAC and a PB were useful to highlight the potential signs of infection and PML, only a minority of them learned about these potential adverse drug reactions from these documents. They also received other written materials named differently; in most cases, it was probably the patient leaflet. If the participants had to choose only 1 of the proposed educational materials, 71.7% preferred a PAC, a shorted description that is held by the patient at all times and reaches the relevant HCP when needed. Interestingly, all patients who thought a PAC not useful to highlight the potential signs of infection and PML (5%) found a PB helpful because it contained more detailed information for both the patient and their family.



*1 participant treated both for RA and MPA (2 – 5 years), 1 participant treated both for RA and GPA (2 – 5 years)

FIGURE 1. Type of rituximab treatment and its duration.

Most significantly, the study demonstrated the importance for these patients to have accessible, updated educational materials in both hardcopy and electronic format. Publication of educational materials on the National Competent Authorities' (NCAs) websites could improve transparency, and development of links with patient and consumer organizations could help raise awareness of the NCA role.[31,32] Recent data have shown that educational materials for all authorized medicines were available on the NCAs website in 10 EU countries: Belgium, Czech Republic, Estonia, Spain, Finland, France, Malta, Netherlands, Portugal, and United Kingdom (40%).[34] Other studies also showed that web-based tools can enhance HCP-to-patient communications.[27] As some patients did not receive a PB from their healthcare providers, a reminder for HCPs might improve the distribution of material to patients. This finding is consistent with

TABLE 3. Source of Information on Potential Adverse Effects (Open-Ended Question)

Source	No. Responses*
Healthcare professional	35
Written information	20
Internet	13
PAC	3
Unspecified	3
Educational materials	1
Other patients	1

*More than 1 answer possible.

results of a study assessing awareness and preferences of HCPs for risk communication. This study showed that general practitioners' awareness of the educational materials at 64% is lower than for direct healthcare professional communication (91%) and NCA communications (79%). The preference for an electronic format rather than a hard copy version varied among countries. Of the respondents, 89% considered repetition of messages as useful. General practitioners recognized point-of-care alerts and e-mail as the most preferred alternative communication channels to stay up to date on drug safety issue.[34]

Study Limitations

Overall, strengths and limitations of the type of data collection should be carefully considered on a case-by-case basis depending on the RMMs, safety concerns, and medicine involved.[27] Survey studies have several limitations, but they can provide valuable insights for outcomes for which studies using secondary data might not be feasible.[11]

Timing of effectiveness evaluation could have been done earlier as educational materials were approved in 2009, whereas the targeted population has been using them for years since the impact of the 2012 EU pharmacovigilance legislation on additional RMM.[1,3] Data collection could be seen as a relatively brief (less than 2 months) period including the year-end holidays. There was limited time to collect survey responses because of the timeframe of the ongoing safety review of the risks of PML and infections and the need to discuss results of this survey at the plenary PRAC December and February meetings.

The conciseness of the survey likely increases the number of respondents, data quality, and completeness.[11,35] Therefore, this questionnaire was focused only on patients understanding and preferences related to important selected risks and not to all adverse effects described in the product information. The high positive response rate of Q1 could be affected by question design but also because of the fact that patients are treated on a long-term basis and could be very well educated. Open-ended questions allowed the respondents to add their own comments, which add rich additional qualitative information but are not always easy to analyze and aggregate.[35] Despite broad interest in the collection and use of patient preferences, some challenges relate to methodological questions concerning the selection bias, validity, reliability, lack of specific guidance, and ensuring patient understanding in these studies,[10] cited in the Food and Drug Administration website.[35,36] One of the limitations of this survey is that being anonymous, it was not possible to validate who the respondents were; in addition, if sociodemographic data as the education level will be collected, it could impact education format preferences. A larger sample size representing more EU countries would be needed to be able to generalize the results further and to draw more robust conclusions. However, recruitment is usually challenging in surveys—sometimes not reaching the prespecified sample size or limited to specific confidentiality regulations, which could exclude some countries.[11] Furthermore, the nature of dissemination and online-only availability of the survey may have favored responders who had access to the Internet, and because the survey was only available in English, it limited participants to those who speak and understand English across Europe. As more than half the respondents came from the United Kingdom (native language), it suggested that language played a major part in the recruitment of respondents. In addition, the participants' countries of residence were limited to those countries that seem to participate more often in these kinds of surveys like United Kingdom or the Netherlands.[11,26] Finally, 18.3% of the participants were from non-EU countries where different pharmacovigilance tools to minimize those risks could have been approved, e.g., in the United States, the medication guide, in addition to existing labeling, which is available in [36]. On the other hand, this disproportionate participation may be also a reflection of the usage of the product.[11] Overall results will not change if we focus only at the responses from the United Kingdom and Ireland (42 of 61) to exclude potentially better educated respondents from non-English native countries in the data set. Most patients were aware of the potential adverse effects (30 versus 12) and were informed by HCPs. Most of them found a PAC (39) and a PB (41) to be useful tools to highlight the potential signs of infection and PML. In case they have to select the 1 educational tool, 31 of them preferred a PAC.

CONCLUSIONS

Because additional RMMs are developed for each medicine independently, a general "criterion standard" set of measures cannot be defined.[27] For this reason, each RMP, together with follow-up assessments, requires careful consideration by the PRAC. Gathering the experience and views of all stakeholders helps ensure that the proposed measures are as relevant and meaningful as possible. This will increase patients' trust in the regulators work and ultimately their uptake of the proposed measures. Educational materials should be used as a tool to increase understanding of safety information between patients and HCPs.[9] Studies focusing on patient preferences could support periodic evaluation of the effectiveness of RMMs and gather acquire suggestions for improvement. Challenges remains in the surveys design, conduct, and interpretation of the results. Considering all the limitations of this survey, this should be seen as an initial step to a broader investigation that has more generalizability and connection to patient safety outcomes.

ACKNOWLEDGMENTS

The authors thank the study participants for their time in completing this survey.

REFERENCES

1. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module XVI—risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). March 31, 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf. Accessed July 29, 2021.
2. Prieto L, Spooner A, Hidalgo-Simon A, et al. Evaluation of the effectiveness of risk minimization measures. *Pharmacoepidemiol Drug Saf*. 2012;21:896–899.
3. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP) Module V—risk management systems (Rev 2). March 31, 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf. Accessed July 29, 2021.
4. Zomerdijk IM, Sayed-Tabatabaei FA, Trifiro G, et al. Risk minimization activities of centrally authorized products in the EU: a descriptive study. *Drug Saf*. 2012;35:299–314.
5. Rubino A, Artime E. A descriptive review of additional risk minimisation measures applied to EU centrally authorised medicines 2006–2015. *Expert Opin Drug Saf*. 2017;16:877–884.
6. European Medicines Agency. European public assessment report for MabThera. February 27, 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf. Accessed July 29, 2021.

7. European Medicines Agency. MabThera: EPAR—risk-management-plan summary. March 16, 2020. Available at: https://www.ema.europa.eu/en/documents/rmp-summary/mabthera-epar-risk-management-plan-summary_en.pdf. Accessed July 29, 2021.
8. Brown P, Bahri P. 'Engagement' of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework. *Eur J Clin Pharmacol*. 2019;75:1181–1192.
9. SCOPE Work Package 6 Risk Communication: risk communication on medicines: report from the workshop. June 17, 2016. Available at: https://www.ema.europa.eu/en/documents/other/scope-training-risk-communication-medicines-report-workshop_en.pdf. Accessed July 29, 2021.
10. Janssens R, Huys I, van Overbeeke E, et al. Opportunities and challenges for the inclusion of patient preferences in the medical product life cycle: a systematic review. *BMC Med Inform Decis Mak*. 2019;19:189.
11. Vora P, Artime E, Soriano-Gabarró M, et al. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic register of post-authorization studies. *Pharmacoepidemiol Drug Saf*. 2018;27:695–706.
12. European Medicines Agency. Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations. EMA/637573/2014. October 16, 2014. Available at: https://www.ema.europa.eu/en/documents/other/revised-framework-interaction-between-european-medicines-agency-patients-consumers-their_en-1.pdf. Accessed September 8, 2020.
13. European Medicines Agency. Rules of procedure on the organisation and conduct of public hearings at the Pharmacovigilance Risk Assessment Committee. EMA/363479/2015. April 13, 2020. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/rules-procedure-organisation-conduct-public-hearings-pharmacovigilance-risk-assessment-committee_en.pdf. Accessed July 29, 2021.
14. Food and Drug Administration. Benefit-risk assessment in drug regulatory decision-making. PDUFA VI: fiscal years 2018–2022. July 7, 2020. Available at: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022. Assessed July 29, 2021.
15. Food and Drug Administration. FDA patient-focused drug development guidance series for enhancing the incorporation of the patient's voice in medical product development and regulatory decision making. June 6, 2020. Available at: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. Accessed July 29, 2021.
16. European Medicines Agency. Committee for medicinal products for human use variation assessment report. MabThera Procedure No. EMEA/H/C/000165/II/0062. 2008.
17. European Medicines Agency. Committee for medicinal products for human use variation assessment report. MabThera Procedure No. EMEA/H/C/000165/II/0068. 2010.
18. European Medicines Agency. Committee for medicinal products for human use extension of indication variation assessment report. MabThera Procedure No. EMEA/H/C/000165/II/0079. March 21, 2013. Available at: https://www.ema.europa.eu/en/documents/variation-report/mabthera-h-c-165-ii-79-epar-assessment-report-variation_en.pdf. Accessed on July 29, 2021.
19. European Medicines Agency. European public assessment report for Blitzima. January 13, 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/blitzima-epar-product-information_en.pdf. Accessed July 29, 2021.
20. European Medicines Agency. European public assessment report for Riximyo. January 13, 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/riximyo-epar-product-information_en.pdf. Accessed July 29, 2021.
21. European Medicines Agency. European public assessment report for Ritemvia. October 1, 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/ritemvia-epar-product-information_en.pdf. Accessed July 29, 2021.
22. European Medicines Agency. European public assessment report for Rixathon. October 3, 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/rixathon-epar-product-information_en.pdf. Accessed July 29, 2021.
23. European Medicines Agency. European public assessment report for Truxima. October 11, 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/truxima-epar-product-information_en.pdf. Accessed September 8, 2020.
24. Agyemang E, Bailey L, Talbot J. Additional risk minimisation measures for medicinal products in the European Union: a review of the implementation and effectiveness of measures in the United Kingdom by one marketing authorisation holder. *Pharmaceut Med*. 2017;31:101–112.
25. European Medicines Agency. EMA Safety Committee (PRAC) consultation with patients taking rituximab regarding the educational materials available for risks of infections and PML. December 7, 2018. Available at: https://ec.europa.eu/eusurvey/runner/MabThera_rituximab. Accessed on 16 April 2020.
26. Farcas A, Huruba M, Mogosan C. Study design, process and outcome indicators of post-authorization studies aimed at evaluating the effectiveness of risk minimization measures in the EU PAS Register. *Br J Clin Pharmacol*. 2019;85:476–491.
27. Banerjee AK, Zomerdijk IM, Wooder S, et al. Post-approval evaluation of effectiveness of risk minimisation: methods, challenges and interpretation. *Drug Saf*. 2014;37:33–42.
28. Artime E, Qizilbash N, Garrido-Estepa M, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. *Expert Opin Drug Saf*. 2019;18:443–454.
29. European Medicines Agency. Minutes of Pharmacovigilance Risk Assessment Committee (PRAC) meeting on 26–29 November 2018 (EMA/PRAC/109243/2019) : 5.3.3 Rituximab—MABTHERA (CAP)—EMEA/H/C/000165/II/0152. January 17, 2019. Available at: https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-26-29-november-2018_en.pdf. Accessed July 29, 2021.
30. Hsiao B, Fraenkel L. Patient preferences for rheumatoid arthritis treatment. *Curr Opin Rheumatol*. 2019;31:256–263.
31. de Wit M, Cooper C, Tugwell P, et al. Practical guidance for engaging patients in health research, treatment guidelines and regulatory processes: results of an expert group meeting organized by the World Health Organization (WHO) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Aging Clin Exp Res*. 2019;31:905–915.
32. Radecka A, Loughlin L, Foy M, et al. Enhancing pharmacovigilance capabilities in the EU regulatory network: the SCOPE Joint Action. *Drug Saf*. 2018;41:1285–1302.
33. Martin LR, Williams SL, Haskard KB, et al. The challenge of patient adherence. *Ther Clin Risk Manag*. 2005;1:189–199.
34. de Vries ST, van der Sar MJM, Cupelli A, et al. Communication on safety of medicines in Europe: current practices and general practitioners' awareness and preferences. *Drug Saf*. 2017;40:729–742.
35. van Overbeeke E, Whichello C, Janssens R, et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. *Drug Discov Today*. 2019;24:57–68.
36. Food and Drug Administration. Prescribing information for Truxima (rituximab). November 1, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761088s000lbl.pdf. Accessed July 29, 2021.