HHS Public Access

Author manuscript

Am Heart J Plus. Author manuscript; available in PMC 2024 February 16.

Published in final edited form as:

Am Heart J Plus. 2024 February ; 38: . doi:10.1016/j.ahjo.2024.100359.

Assessment of the U.S. Food and Drug Administration's risk evaluation and mitigation strategy (REMS) for prasugrel (EFFIENT): A narrative review

Thomas Metkus[a], **Jill Curran**[b,c], **Shanshan Lin**[b,c], **Dima M. Qato**[d,e], **G. Caleb Alexander**[b,c,f,*]

[a]Division of Cardiology and Cardiac Surgery, Departments of Medicine and Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[b]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[c]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[d]Program on Medicines and Public Health, Titus Family Department of Clinical Pharmacy, University of Southern California School of Pharmacy, Los Angeles, California, USA

[e]Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, California, USA

[f]Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA

Abstract

Background: Prasugrel, first approved in 2009, was subject to a US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of bleeding associated with its use.

Methods: We performed a narrative review of FDA documents obtained through a Freedom of Information Act request. Document classification and primary evidence extraction was performed by three authors (TM, JC, and SL).

Results: The prasugrel REMS consists of a medication guide and a communication plan. Assessment of the REMS was via patient and clinician surveys. 1560 patients were invited

*Corresponding author at: Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street W6035, Baltimore, MD 21205, USA. galexan9@jhmi.edu (G.C. Alexander).

CRediT authorship contribution statement

Thomas Metkus: Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jill Curran:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Shanshan Lin:** Investigation, Writing – review & editing. **Dima M. Qato:** Conceptualization, Writing – review & editing. **G. Caleb Alexander:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100359.

to participate and 212 individuals (13.6 %) completed the survey. Rates of awareness among respondents varied across key messages and were highest for those examining the risks of premature discontinuation (96 % and 88 % of respondents), while lower for those regarding the importance of perioperative discontinuation (66 %) and contraindications posed by a history of stroke (16 %) or transient ischemic attack (17 %). Of the 6000 clinicians invited to participate in the survey, 201 (3.4 %) agreed to take part. Four of 11 key risk messages did not meet prespecified acceptable levels of comprehension. No prespecified levels of patient or provider knowledge were required for the retirement of the REMS, which took place on March 23, 2012 based on the sponsor's request.

Conclusions: The prasugrel REMS consisted of passive educational materials whose adequacy was evaluated using highly limited, one-time, cross-sectional surveys. Our assessment adds to evidence suggesting the importance of improving the quality and impact of the FDA's post-approval activities to maximize drug safety.

Keywords

U.S. Food and Drug Administration; Risk evaluation and mitigation programs; Drug risks

1. Background

Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist first approved by the U.S. Food and Drug Administration (FDA) in 2009 for the reduction of acute myocardial infarction in individuals with acute coronary syndrome after percutaneous coronary intervention (PCI). Despite its efficacy as an anti-platelet agent, it is associated with an increase in major bleeding, especially among individuals with prior stroke, aged 75 years or older, or who weigh 60 kg or less [1,2].

Since optimizing prasugrel's use may require complex risk/benefit tradeoffs, in addition to a boxed warning instituted with approval in 2009, the FDA mandated that the drug's manufacturer institute a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval. REMS are used by the FDA to help optimize the value of medications with serious safety concerns; these programs focus on preventing, monitoring, and managing serious risks.

Many evaluations of REMS have been performed [3–6] and the FDA's REMS program has also been subject to broader review, both by individual investigators [7,8] as well as the Office of the Inspector General [9]. While systematic shortcomings in the structure and function of the program have been identified [9], assessments of REMS for specific products have yielded variable results. In some cases, REMS have been associated with significant reductions in potentially unsafe prescription drug use [5], while in other cases, REMS programs have been so limited in their design or execution that their success has not been able to be assessed [4], while in yet other cases, such evaluations have suggested no impact [3].

Given the widespread use of prasugrel and other anti-platelet agents, as well as continued interest in understanding the structure and function of the FDA's risk mitigation activities,

we used a Freedom of Information Act (FOIA) request to obtain documents from the FDA regarding the design and evaluation of the prasugrel REMS. We were especially interested how prasugrel's manufacturer and the FDA designed and assessed the effectiveness of the REMS program to improve prasugrel's safe use, as well as the rationale for the termination of the program in 2012.

2. Methods

2.1. Study design and FOIA history

We used a FOIA request to obtain documents from the FDA related to institution and assessment of and decision to retire the prasugrel REMS. We specifically requested documents related to the components of the REMS, final agreed-upon REMS, REMS assessments and decision to release the REMS. On July 14, 2022 the FDA provided 850 pages of documents including some which were redacted based on the exceptions for "confidential commercial information" [5 USC §552 (b)(4)] and/or "unwarranted invasion of personal privacy" [5 USC §552 (b)(6)]. After appeal, 459 additional pages of unredacted documents were provided between October 12 and December 15, 2022. However, 191 of these additional pages were duplicates, resulting in 268 total new pages released after the initial production. In February 2023 we received 543 pages of additional documents related to advisory committee records. Materials were obtained with assistance of the Yale Law School Collaboration for Research Integrity and Transparency.

2.2. Document review and analysis

The REMS goal to mitigate the risk of bleeding associated with prasugrel was to be reached by: (1) informing patients of the serious risks associated with prasugrel, particularly the increased risk of bleeding; and (2) communicating the increased risk of bleeding and the need for appropriate patient selection to prescribers. These goals were to be obtained through REMS elements including a medication guide and communication plan, and to include assessments of the impact of these interventions (Table 1), including health care provider and patient surveys [10].

We extracted information from the documents we received from the FDA related to these REMS elements and any evaluations that were conducted to assess whether the goals of the REMS were being met. Three authors (TM, JC and SL) independently reviewed each document and extracted relevant information, while additional document review was performed by an additional author (GCA). Throughout this process, the authors met together to review findings from the iterative review of the source documents and build consensus regarding the analysis and interpretation of results. All primary survey analyses were performed by other parties, including the sponsor and FDA, and thus no new quantitative analyses were performed by the authors.

Our study was exempt from review by the Johns Hopkins University Institutional Review Board as it did not constitute human subjects research.

3. Results

3.1. Structure of prasugrel's REMS

Prasugrel's medication guide was available for distribution with each prescription, and it was meant to advise patients about the risk of bleeding and also inform patients of prasugrel's contraindications, including drug-drug interactions and risk factors such as patient age greater to or equal than 75 years and body weight <60 kg. The medication guide was also meant to inform patients of the signs and symptoms of bleeding requiring immediate medical attention along with the necessity to discontinue prasugrel prior to elective surgery.

Prasugrel's communication plan consisted of an informational "Dear Healthcare Prescriber" (DHCP) letter as well as a prescriber brochure sent to clinicians likely to use prasugrel. The issuance of the letter was set to occur within 45 days of product approval and was completed between July 20, 2009 and August 8, 2009, while the prescriber brochure was disseminated during the first sales representative visit to a given prescriber for the first two years after launch of the product. The purpose of the letter was to inform healthcare providers of the serious bleeding risks and the importance of appropriate use among the proper patient population. The prescriber brochure aimed to relay key safety messages regarding the risk of bleeding and its management through guidance on proper patient selection. It also provided information for prescribers to discuss with patients.

The Sponsor and FDA agreed that the sponsor would perform patient and health care provider surveys to evaluate whether the medication guide and communication plan were sufficient to meet the REMS' goals. The surveys, which were to be submitted to the FDA at 18 months, 3 years, and 7 years after REMS approval, were intended to assess patients' understanding of the serious risks of prasugrel along with their understanding of the medication guide, while the provider survey was designed to assess prescribers" understanding of the safety messages and adherence to its boxed warning. Additionally, if the surveys indicated patient or prescriber awareness was not adequate, the sponsor was required to specify activities to increase awareness. The sponsor initially submitted the REMS in December 2007, and after 3 modifications, the initial REMS was instituted in July of 2009 (Fig. 1).

3.2. Patient survey to assess understanding of prasugrel's risks

3.2.1. Survey design—The patient survey sampled individuals age 18 years or older receiving prasugrel within the past 90 days. It was pretested and piloted to enhance face and construct validity among intended participants, and to ensure its appropriateness for individuals of varying literacy levels. Individuals were recruited through retail pharmacies and healthcare provider offices using both a telephonic interactive voice response system as well as mailed letters directing individuals to an internet-based survey platform. A target sample size of 200 completed surveys was established with a goal comprehension rate of 80 % or higher on key questions regarding prasugrel's safety and appropriate conditions of use, and individuals were offered a $25 gift card upon survey completion [11].

3.2.2. Survey outcome—A total of 1560 patients were invited to participate in the survey, 60 of whom were invited through an interactive voice response system and 1500 through mailed letters. Of these, 234 individuals opted for screening, which involved logging onto the survey website or calling the survey coordinating center to provide a valid unique code, 1 of whom was deemed ineligible. Of the remaining 233 individuals, 212 completed the survey, of whom 211 were current prasugrel users, with 86 % of participants reporting use for at least one month. Eligibility criteria included: age 18 years or older; prasugrel use within 90 days of the survey; and ability to read, respond, and complete the survey in English. Most survey respondents were male (72 %), had completed at least some college education (70 %), nearly all reported speaking primarily English at home (98 %) and were concentrated in the Midwest (42 %) or Southern (37 %) United States [11].

Approximately two-thirds of respondents (69 %) reported having received a prasugrel medication guide, and of these, four-fifths (80 %) reported having read it. Of those having received and read the guide, 82 % reported reading all or most of it and 84 % reported understanding all or most of it. During the patient survey, 8 individuals reported active questions about the medication guide.

The patient survey evaluated nine key risk messages, three focused on the increased bleeding risk, three focused on the medical conditions and concomitant medications that could increase bleeding risk, and two focused on risks of early discontinuation and the importance of consulting with a prescriber before discontinuing prasugrel (Table 2). Rates of awareness among respondents varied across key messages and were highest for those examining the risks of premature discontinuation (96 % and 88 %), while lower for those regarding the importance of perioperative discontinuation (66 %) and contraindications posed by a history of stroke (16 %) or transient ischemic attack (17 %).

3.3. Healthcare provider assessment of prasugrel's risks

3.3.1. Survey design—Using the communication plan mailing list, a random sample of prescribers were invited by U.S. mail to participate in an internet-based survey or telephone survey facilitated by a trained interviewer. Prescribers were offered a $75 honorarium to participate and stratified into interventional cardiologists, clinical cardiologists, primary care physicians, and other providers. As with the patient survey, a target sample size of 200 completed surveys was established to allow for estimation of the target comprehension rate of 80 % for each risk message.

3.3.2. Survey outcome—A total of 6000 invitation letters were sent, with 201 providers agreeing to participate between September and November 2010. Most respondents were male (84 %), had practiced for at least eleven years (73 %) and were interventional (31 %) or non-interventional (56 %) cardiologists. Of respondents, 181 were prescribers, two-thirds (63 %) had been prescribing prasugrel for 6–12 months and most from the Northeastern (32 %) or Southern (34 %) United States.

About one-third of respondents (29 %) reported having received the DHCP letter, whereas approximately one-half (48 %) reported having received the prescriber brochure. However, a higher percentage of respondents reported reading at least some of these documents (49

% DHCP letter and 73 % prescriber brochure) than the percentage reported having actually received them.

The survey examined 11 risk messages including populations with higher background risk of bleeding, specific contraindications, and strategies to manage perioperative use (Table 3). For seven of these eleven key risk messages, >80 % of respondents answered the items correctly. By contrast, for four messages, including 3 covering the circumstances when prasugrel should or should not be discontinued and 1 regarding adjusting dosage based on weight, a lower proportion of respondents indicated knowledge, ranging from 49 % to 71 % [12].

3.4. First assessment of prasugrel REMS (submitted January 2011)

3.4.1. Sponsor interpretation of patient and provider surveys—The first REMS assessment reported the distribution of the medication guide and communication plan as well as analysis of patient and provider surveys (Table 1) [13]. The sponsor concluded that REMS materials had been distributed per the REMS mandate, and that patients understood prasugrel's main risk is bleeding and were able to identify the signs and symptoms that should prompt medical attention. The sponsor also speculated regarding the basis for low understanding of some risks, ranging from poor wording of some survey items to failure of pharmacists to dispense medication guides to deficiencies in patient-provider communication; the assessment noted that additional qualitative testing would be performed to understand these root causes. For the HCP survey, the sponsor again concluded that respondents showed an understanding of the overall risks of bleeding, contraindications, and a general understanding of the risks within the boxed warning, while noting potentially confusing survey item construction and inappropriate parsing of key risk messages among the survey questions as the possible basis for lower understanding of some risks. Low response rates were not referenced in the discussion.

3.4.2. Sponsor's proposed actions based on patient and provider survey results—Notwithstanding their conclusion that no immediate changes were required in the medication guide nor communication plan, the sponsor nevertheless suggested a series of steps to be undertaken based on the results of the patient and provider surveys. First, they proposed to improve the surveys through further piloting and pretesting using individual participants and/or focus groups. Second, the sponsor proposed to reevaluate the suitability of using an 80 % threshold as the target correct response in consultation with FDA. Third, they proposed qualitative testing to help determine whether the communication of risk messages in the medication guide could be improved.

3.4.3. FDA proposed actions based on patient and provider survey results—In reviewing the 18-month REMS assessment, the FDA expressed concern regarding the low number of patients correctly reporting prasugrel's contraindication among individuals with a history of TIA or stroke. The Sponsor proposed to revise the medication guide to address this, and in June 2011, the Sponsor included, and FDA approved, revisions to the REMS including changes to the medication guide and prescriber's brochure to increase the text regarding stroke/TIA contraindication and also to add hypersensitivity following label

changes made adding this to the warnings and precautions section of the label. No specific changes were recommended regarding individuals who did not receive or read the materials.

3.5. Discontinuation of prasugrel risk evaluation and mitigation strategies (REMS)

In February 2012 the Sponsor requested that prasugrel's REMS be discontinued [14]. They noted that communication plan had been discontinued in July 2011 since it was only required for two years following launch, and argued that the information within the medication guide could be continued as part of the approved labeling without requiring a REMS. In March of 2012, the FDA approved this request and the REMS was retired [15].

4. Discussion

Antiplatetet agents reduce ischemic events at the cost of bleeding risk, especially among some patient groups [16]. In this narrative review of FDA documents obtained using a FOIA request, we examine the program that prasugrel's manufacturer and the FDA used to promote its safe use. The prasugrel REMS consisted of educational information communicated passively to patients and prescribers, whose adequacy was assessed using cross-sectional surveys of small and potentially highly selective samples. Taken together, our work illuminates the REMS process for this widely used antiplatelet agent and our findings suggest the importance of improved development and assessment of communication strategies to improve safe drug use as part of the FDAs post-marketing requirements.

Despite the important risk messages contained with prasugrel's communication plan, the sponsor disseminated these risk messages using methods of risk communication with known limitations [17,18]. For example, a review of medication guides suggests that they are generally complex and unhelpful to patients in most cases [18–21]. Similarly, the DHCP letter consisted of a one-time prescriber letter, without any mechanism to ensure clinician engagement. There are a variety of methods that could have been used to augment passive delivery of educational materials such as these, including electronic communication [22,23], academic detailing [24,25], engagement with professional societies and guideline committees and multimedia dissemination of best practices. Electronic decision support aids also have the potential to augment these educational ventures, although we are not aware of their use by sponsors to fulfill post-marketing requirements imposed by the FDA.

The means that prasugrel's manufacturer and the FDA used for assessment of the REMS educational program was also quite limited. First, the surveys were cross-sectional and lacked any comparison group, preventing an even rudimentary ability to assess for changes in knowledge and comprehension of patients or providers over time. Second, the response rates to the patient and prescriber surveys were incredibly low, and in the documents that we reviewed, neither the sponsor nor FDA considered the validity threats posed by non-response bias, nor methods of ascertaining the magnitude of such bias such as through the comparision of respondents with non-respondents on any known characteristics. Third, the methods of assessment were qualitative and overall lacking in rigor. Despite these limitations, the survey nevertheless suggested sub-optimal clinician and patient understanding of important facets of prasugrel management, particularly around perioperative management and a contraindication with prior stroke and TIA.

Interestingly, the FDA discontinued the prasugrel REMS after almost three years. The REMS was discontinued on the basis of the components having been satisfied or dropped from the REMS program. The prasugrel REMS had two components, the communication plan and the medication guide. Since the communication plan was only required for two years, that component was satisfied within two years of the REMS being implemented. There were no requirements other than simply executing the communication plan for that time period. FDA removed medication guides from REMS programs in 2011 since the guides became a requirement for product labeling [26,27]. When this happened, any existing REMS programs that consisted of only a medication guide could be released. Once the two years of the communication plan were satisfied, the prasugrel REMS consisted only of the medication guide and therefore, was released upon request by the Sponsor. The REMS did not require any of the REMS evaluations, including the patient and prescriber surveys, to meet any specific goals in order for the REMS to be released. Additionally, we did not find further correspondence regarding the Sponsor and FDA regarding the results of the surveys and the proposed actions to remediate any suboptimal understanding of risk exposed during these surveys once the REMS was discontinued.

Antiplatelet and anticoagulant products are logical ones for REMS, since these products account for a high proportion of drugs causing serious adverse events [28]. In addition, as with other products subject to REMS programs, these are ones whose risk/benefit profile depends crucially upon patient selection [29,30]; a foundational concept in the use of these drug classes is the important tradeoff between reduction in ischemic and increase in bleeding events. FDA post-marketing requirements, when instituted to improve safe use, should include decision aids that assist patients and providers in optimal drug usage. REMS assessments should also include both qualitative assessment of clinician knowledge and quantitative assessments of prescription patterns derived from electronic health information. Decision support and electronic passive and active survey systems, such as those used successfully for cardiac devices, are attractive monitoring constructs [31], although even with surveys, there are novel mechanisms to increase survey response rates including electronic implementation [32], participant incentive choice [33], and incentive amount [34], and broad and multimodal outreach and ensuring sampling of diverse socioeconomic populations with appropriate weighting should be undertaken.

Our analysis has several limitations. First, our review is based on documents obtained through a FOIA, some of which were redacted, and it is possible that relevant documents in the FDA’s possession were not provided for our review. Second, our assessments of patient and prescriber knowledge are inherently limited by the nature of the surveys themselves, as we describe above. Third, as with all qualitative analyses, our findings and interpretations may be shaped by our own preconceptions, although we used several methods to minimize this validity threat [35]. Finally, we evaluated a program that was discontinued more than a decade ago, and REMS have continued to evolve. However, more recent REMS evaluations support our findings and substantive interpretation [9,36], and the principles we consider are relevant to future REMS design.

5. Conclusions

Antiplatelet agents are emblematic of the risks and benefits that must often be balanced when using therapeutics. In this review of the post-marketing commitments imposed upon prasugrel's manufacturer by the FDA, we found the REMS program consisted of passive educational materials whose adequacy was evaluated using highly limited, one-time, cross-sectional surveys. Our assessment is based on reviews of documents that are typically not publicly disclosed by sponsors or the FDA [37], and it adds to evidence suggesting the importance of continued efforts to improve the quality and impact of the FDA's post-approval activities to improve drug safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors gratefully acknowledge the assistance of Cortelyou Kenney, JD, and Margaret McCarthy, MA, JD, PhD, of the Yale Law School Collaboration for Research Integrity and Transparency for assistance obtaining the materials examined. They did not receive compensation for their role in the study.

References

[1]. Angiolillo DJ, Bates ER, Bass TA, Clinical profile of prasugrel, a novel thienopyridine, Am. Heart J 156 (2 Suppl) (Aug 2008) S16–S22. [PubMed: 18657682]

[2]. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators, Prasugrel versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med 357 (20) (Nov 15, 2007) 2001–2015. [PubMed: 17982182]

[3]. Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC, Assessment of the FDA risk evaluation and mitigation strategy for transmucosal immediate-release fentanyl products, JAMA 321 (2019) 676–685. [PubMed: 30778596]

[4]. Heyward J, Olson L, Sharfstein JM, Stuart EA, Lurie P, Alexander GC, Evaluation of the extended-release/long-acting opioid prescribing risk evaluation and mitigation strategy program by the US Food and Drug Administration: a review, JAMA Intern. Med 180 (2020) 301–309. [PubMed: 31886822]

[5]. Brandenburg NA, Bwire R, Freeman J, Houn F, Sheehan P, Zeldis JB, Effectiveness of risk evaluation and mitigation strategies (REMS) for lenalidomide and thalidomide: patient comprehension and knowledge retention, Drug Saf. 40 (2017) 333–341. [PubMed: 28074423]

[6]. Amend KL, Younus M, Petronis KR, Mo J, Seeger JD, Gately R, Gu X, Enger C, Assessment of risk evaluation and mitigation strategies (REMS) for varenicline (Chantix): a multistage patient survey, Pharmacoepidemiol. Drug Saf 27 (2018) 253–262. [PubMed: 29405516]

[7]. Guadamuz JS, Qato DM, Alexander GC, Use of risk evaluation and mitigation strategies by the US Food and Drug Administration, 2008–2019, JAMA 324 (2020) 299–301. [PubMed: 32692379]

[8]. Qato DM, Alexander GC, Improving the Food and Drug Administration's mandate to ensure postmarketing drug safety, JAMA 306 (2011) 1595–1596. [PubMed: 21990303]

[9]. Office of Inspector General, US Department of Health and Human Services. FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety. https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf. Published 2013. Accessed January 24, 2023.

[10]. Risk Evaluation and Mitigation Strategy (REMS). Submitted to the US Food and Drug Administration on January 31, 2011. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

[11]. Quantitative Testing of Patient Knowledge of the EFFIENTTM (prasugrel) Tablet Risk Evaluation and Mitigiation Strategy. Submitted to the US Food and Drug Administration on January 12, 2011. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received October 2022).

[12]. Quantitative Testing of Prescriber Knowledge of the EFFIENTTM (prasugrel) Tablet Risk Evaluation and Mitigiation Strategy. Submitted to the US Food and Drug Administration on January 12, 2011. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received October 2022).

[13]. 18-month Risk Evaluation and Mitigation Strategy (REMS) Assessment. Submitted to the US Food and Drug Administration on January 31, 2011. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

[14]. Proposed REMS Modification – Request to Remove Effient Medication Guide From REMS. Submitted to the US Food and Drug Administration on February 03, 2012. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

[15]. US Food and Drug Administration. Supplemental Approval Release REMS Requirement. March 23, 2012. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

[16]. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR, Gersh BJ, Shah ND, Noseworthy PA, Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation, J. Am. Heart Assoc 5 (2) (Feb 23, 2016) e003074, 10.1161/JAHA.115.003074. 26908412. [PubMed: 26908412]

[17]. Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH, Communicating safety information to physicians: an examination of dear doctor letters, Pharmacoepidemiol. Drug Saf. 14 (12) (Dec, 2005) 869–875.

[18]. Wolf MS, Davis TC, Shrank WH, Neuberger M, Parker RM, A critical review of FDA-approved medication guides, Patient Educ. Couns 62 (3) (Sep 2006) 316–322. [PubMed: 16884888]

[19]. Allen LaPointe NM, Pappas P, Deverka P, Anstrom KJ, Patient receipt and understanding of written information provided with isotretinoin and estrogen prescriptions, J. Gen. Intern. Med 22 (1) (Jan 2007) 98–101. [PubMed: 17351847]

[20]. Knox C, Hampp C, Willy M, Winterstein AG, Dal Pan G, Patient understanding of drug risks: an evaluation of medication guide assessments, Pharmacoepidemiol. Drug Saf 24 (2015) 518–525. [PubMed: 25808393]

[21]. Wolf MS, King J, Wilson EA, Curtis LM, Bailey SC, Duhig J, Russell A, Bergeron A, Daly A, Parker RM, Davis TC, Shrank WH, Lambert B, Usability of FDA-approved medication guides, J. Gen. Intern. Med 27 (12) (Dec 2012) 1714–1720. [PubMed: 22566170]

[22]. Huston J, Adler E, Simon J, Dear doctor letters: lessons in statutory interpretation, preemption, proximate causation, and subsequent-remedial measures, Ann. Health Law 22 (2) (2013) 445–479.

[23]. Piening S, de Graeff PA, Straus SM, Haaijer-Ruskamp FM, Mol PG, The additional value of an E-mail to inform healthcare professionals of a drug safety issue: a randomized controlled trial in the Netherlands, Drug Saf. 36 (9) (Sep 2013) 723–731. [PubMed: 23797603]

[24]. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, Forsetlund L, Bainbridge D, Freemantle N, Davis DA, Haynes RB, Harvey EL, Educational outreach visits: effects on professional practice and health care outcomes, Cochrane Database Syst. Rev 2007 (4) (Oct 17, 2007) CD000409. [PubMed: 17943742]

[25]. Avorn J, Academic detailing: "marketing" the best evidence to clinicians, JAMA 317 (4) (Jan 24, 2017) 361–362. [PubMed: 28118458]

[26]. Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies. https://www.fda.gov/media/79776/download. Published 2022. Accessed June 20, 2023.

[27]. Guadamuz JS, Qato DM, Alexander GC, Use of risk evaluation and mitigation strategies by the US Food and Drug Administration, 2008–2019, JAMA 324 (2020) 299–301, 10.1001/jama.2020.6611. [PubMed: 32692379]

[28]. Budnitz DS, Lovegrove MC, Shehab N, Richards CL, Emergency hospitalizations for adverse drug events in older Americans, N. Engl. J. Med 365 (21) (Nov 24, 2011) 2002–2012. [PubMed: 22111719]

[29]. Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC, Assessment of the FDA risk evaluation and mitigation strategy for transmucosal immediate-release fentanyl products, JAMA 321 (2019) 676–685. [PubMed: 30778596]

[30]. Kuijer PM, Hutten BA, Prins MH, Büller HR, Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism, Arch. Intern. Med 159 (5) (Mar 8, 1999) 457–460. [PubMed: 10074953]

[31]. Resnic FS, Majithia A, Marinac-Dabic D, Robbins S, Ssemaganda H, Hewitt K, Ponirakis A, Loyo-Berrios N, Moussa I, Drozda J, Normand SL, Matheny ME, Registry-based prospective, active surveillance of medical-device safety, N. Engl. J. Med 376 (6) (Feb 9, 2017) 526–535. [PubMed: 28121489]

[32]. Meena R, Sharma R, Malhotra V, Rathore PK, Comparison of trans-septal suturing technique with polyvinyl alcohol sponge-based nasal packing for hemostasis in septoplasty, Cureus 14 (5) (May 20, 2022) e25161. [PubMed: 35747004]

[33]. Turnbull AE, O'Connor CL, Lau B, Halpern SD, Needham DM, Allowing physicians to choose the value of compensation for participation in a web-based survey: randomized controlled trial, J. Med. Internet Res 17 (7) (Jul 29, 2015) e189. [PubMed: 26223821]

[34]. Halpern SD, Ubel PA, Berlin JA, Asch DA, Randomized trial of 5 dollars versus 10 dollars monetary incentives, envelope size, and candy to increase physician response rates to mailed questionnaires, Med. Care 40 (9) (Sep, 2002) 834–839. [PubMed: 12218773]

[35]. Malterud K, Qualitative research: standards, challenges, and guidelines, Lancet 358 (9280) (Aug 11, 2001) 483–488. [PubMed: 11513933]

[36]. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on health sciences policy; committee on pain management and regulatory strategies to address prescription opioid abuse, in: Phillips JK, Ford MA, Bonnie RJ (Eds.), Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use, National Academies Press (US), Washington (DC), Jul 13, 2017, 6, Opioid Approval and Monitoring by the U.S. Food and Drug Administration. Available from: https://www.ncbi.nlm.nih.gov/books/NBK458654/.

[37]. Sharfstein J, Miller J, Davis A, Ross J, McCarthy M, Smith B, Chaudhry A, Alexander GC, Kesselheim A, Blueprint for transparency at the U.S. Food and Drug Administration: recommendations to advance the development of safe and effective medical products, J. Law Med. Ethics 45 (S2) (2017) 7–23.

[38]. Corrected REMS Communication Documents – Dear Health Care Professional. Submitted to the US Food and Drug Administration on July 14, 2009. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

[39]. Effient Prescriber's Overview. Submitted to the US Food and Drug Administration on January 31, 2011. (Obtained under the Freedom of Information Act from US Food and Drug Administration; requested as FDA FOIA 2019–4465 May 2019; received July 2022).

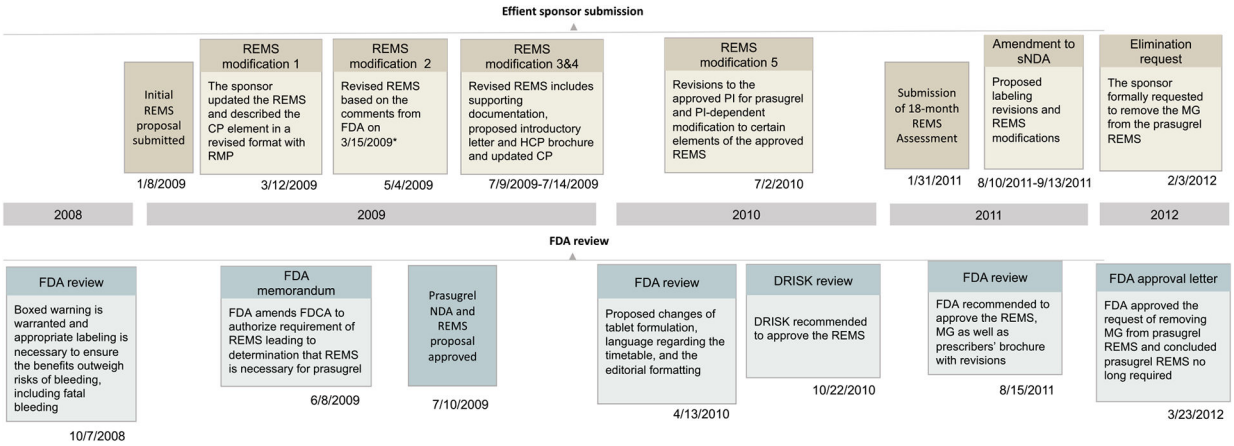

Fig. 1.

Timeline of communications between prasugrel sponsors and the US Food and Drug Administration (FDA).

Note: RMP, risk management plan; MG, Medication Guide; CP, Communication Plan; HCP, Healthcare Provider; PI, Prescribing Information; DRISK, Division of Risk Management.

Table 1

Results of medication guide distribution assessment and communication plan assessment from the first REMS assessment.

Medication guide distribution assessment	
Manufacturing process	No manufacturing deviations were observed/identified that would indicate that the Medication Guide was not distributed in accordance with 21 CFR 208.24
Control strategy	No change controls were implemented for the control strategy for ensuring the Medication Guide is included in packaging
Product complaint	One for missing literature/leaflet on bottled product and one for insufficient numbers of literature/leaflet with blistered product
Conclusion	The assessment indicates that distribution is occurring as required with no systematic issues identified
Communication plan assessment	
Components[a]	Dear Healthcare Provider (DHCP) letter and a prescriber brochure
DHCP letter	The letter was issued via registered email or postal mail to member physicians and via the US postal service to non-member physicians with 94.4 % delivery rate overall
Prescriber brochure	Disseminated during the first sales representative visit for the first two year after launch
Conclusion	The distribution reports indicate that the DHCP letter and prescriber's brochure have been distributed per the commitment

Note:

[a]Dear Healthcare Provider (DHCP) letter was a one-time event on the marketplace introduction of prasugrel; the distribution of the prescriber brochure lasted for two years after launch.

Am Heart J Plus. Author manuscript; available in PMC 2024 February 16.

Table 2

Results of September 7 through October 5, 2010 patient survey assessment from the first REMS assessment.

Patients' understanding of the serious risk of Effient[a]		
Key risk message, KRM	**Correct response rate, CRR, n (%) (*N* = 212)**	**Sponsor's comment**
1. Patients taking EFFIENT may have an increased risk of bleeding which can be serious and sometimes lead to death	171(81)	The patients achieved the targeted CRR
2. Patients who are treated with angioplasty and have a stent, and stop taking EFFIENT too soon, have a higher risk of a blood clot in the stent, having a heart attack, or dying	187 (88)	The patients achieved the targeted CRR
3. Patients should not take EFFIENT if they currently have abnormal bleeding such as stomach or intestinal bleeding, or bleeding in their head	159 (75)	The CRR was within 10 % of the prespecified threshold, with only 1.4 % of respondents responding with wrong answer. Also, patients achieve the targeted CRR for signs and symptoms of bleeding being asked in KRM 8. Therefore, the sponsor believe that it will not impact the appropriate use of Effient
4. Patients should not take EFFIENT if they have a history of stroke or "mini stroke" (also known as a transient ischemic attack or TIA)	34 (16)	Patients may not be aware of the contraindication because they assume that their physician is prescribing the drug in accordance with the approved label and almost all the physicians in the HCP survey were aware of the contraindication for prior TIA/stroke with 98 % of CRR. Therefore, the sponsor believe that it will not have high impact on the appropriate use of Effient
5. Patients should stop taking EFFIENT if they have a stroke	35 (17)	The sponsor will assess this KRM via further qualitative testing and review of the Medication Guide to determine if improvements are needed
6. Patients may have a higher risk of bleeding while taking EFFIENT if they: • have had trauma, such as an accident or surgery • have stomach or intestine bleeding that is recent or keeps coming back • have a stomach ulcer • have severe liver problems • weigh <132 lbs (60 kg) • take other medicines such as Coumadin or Jantoven (warfarin), Heparin, or long-term use of Motrin or Advil (Ibuprofen) or Aleve (Naproxen)	39 (18)	The results for each of the seven individual risk factor survey questions are considered to have varying impact on the appropriate use of Effient,
7. Whenever possible, patients should stop taking EFFIENT at least 7 days before any surgery	140 (66)	The Sponsor will re-evaluate the presentation of this concept through further qualitative testing of the Medication Guide, as well as determining how the survey question was presented and understood by the patients.
8. Patients should call their doctor right away if they have any of these signs of bleeding: • unexpected bleeding or bleeding that lasts a long time • bleeding that is severe or that cannot be controlled	166 (78)	The only three items with CRR below 80 % were listed and the reasons of low CCRR are: • clear urine (76 %): it is possible that patients did not understand what 'clear urine' meant

- pink or brown urine
- red or black stools (looks like tar)
- bruises that happen without a known cause or get larger
- coughing up blood or blood clots
- vomiting blood or vomit that looks like “coffee grounds”

- bruises that happened after getting hit hard (73 %): It is possible that patients may have interpreted this scenario in a context that was different than what the question intended
- mild nausea (76 %): The 11 % of respondents answering wrong possibly erred on side of calling the doctor right away (as opposed to informing their doctor in a less urgent fashion)

9. Patients should not stop taking EFFIENT without talking to their doctor who prescribes it for them	204 (96)	The patients achieved the targeted CRR
Conclusion: Overall, patients demonstrated comprehension of the key risk messages regarding the increased risk of bleeding while taking Effient, the signs and symptoms of bleeding, and to contact their physician prior to discontinuing Effient		
Patients’ understanding of the medication guide		
Conclusion: Survey respondents reported receipt of Medication Guides as follows: 63 % “aware” and 69 % “received”. As manufacturing reports indicate that distribution is occurring as required with no systematic issues identified, the Sponsor believes that no further action is warranted.		

[a]Pre-specified target was to achieve at least an 80 % correct response rate for each Key Risk Message.

Table 3

Results of September 7 through November 14, 2010 healthcare provider survey assessment from the first REMS assessment (n = 201 prescribers).

Key risk message, KRM	Correct response rate CRR, n (%)	Sponsor's comment
1. EFFIENT can cause significant, sometimes fatal, bleeding	190 (95)	Prescribers achieved the targeted CRR
2. EFFIENT is not generally recommended in ≥75-year old patients because they are at higher risk of fatal bleeding and intracranial hemorrhage, except in high risk situations, (diabetes or prior MI), where its effect appears to be greater and its use may be considered	164 (82)	Prescribers achieved the targeted CRR
3. Do not start EFFIENT in patients likely to undergo urgent coronary artery bypass graft surgery (CABG)	169 (84)	Prescribers achieved the targeted CRR
4. Whenever possible, discontinue EFFIENT at least 7 days prior to any surgery	120 (60)	Sponsor believes question may not have been clear and decides to re-evaluate how item was presented and understood
5. EFFIENT should generally be discontinued in patients who experience a TIA or stroke	142 (71)	Sponsor will perform qualitative testing to explore whether the question structure (eg. use of the word "generally") is causing the low correct response rate
6. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of EFFIENT	175 (87)	The prescribers achieved the targeted CRR
7. If possible, manage bleeding without discontinuing EFFIENT. Discontinuing EFFIENT, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events	99 (49)	KRM 7 was delivered by asking two survey questions. It is difficult to answer the first question (56.2 % of CRR) without considering the context that is provided within the second question (88.1 % CRR). The first question includes an element of clinical judgment, whereas the second question specifically tested HCP knowledge regarding the risk of subsequent CV events
8. EFFIENT is contraindicated in patients with active, pathological bleeding such as peptic ulcer or intracranial hemorrhage, or history of prior TIA or stroke	196 (98)	The prescribers achieved the targeted CRR
9. Among patients taking EFFIENT, the following patient populations are at higher risk for bleeding: • patients 75 years of age and older, • patients with a body weight <132 lbs. (60 kg), • patients with a propensity to bleed including those who have had recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, active peptic ulcer disease, severe hepatic impairment, or • patients taking concurrent medications that increase the risk of bleeding such as oral anticoagulants, chronic use of non-steroidal anti- inflammatory drugs (NSAIDs), or fibrinolytic agents	179 (89)	The prescribers achieved the targeted CRR
10. Consider lowering the maintenance dose of EFFIENT to 5 mg daily in patients weighing <132 lbs. (60 kg)	128 (64)	This KRM is not part of the boxed warning; however, prescribers do understand that low body weight <60 kg increases a patient's risk of bleeding which was shown by 81 % of CRR for the body weight item within survey question 5, KRM 9.
11. It is important to instruct patients to get prompt medical attention if they experience any unanticipated, prolonged, or excessive bleeding	200 (100)	The prescribers achieved the targeted CRR