March 8, 2023

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Food and Drug Administration
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Submitted electronically via http://www.regulations.gov.

Re: Docket No. FDA-2022-N-3071- Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments.

Dear Chairperson Lo Re, Chairperson Chodosh, and Advisory Committee members,

Thank you for the opportunity to provide written comments on proposed changes to the iPLEDGE Risk Mitigation and Evaluation Strategy (REMS) requirements to "minimize the existing burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin oral capsules from patients."[1]

The American Academy of Dermatology Association (AADA) represents more than 16,500 dermatologists nationwide. AADA is committed to excellence in the medical and surgical treatment of skin disease, advocating for high standards in clinical practice, education, and research in dermatology and dermatopathology, and driving continuous improvement in patient care and outcomes while reducing the burden of skin disease.[2] As the leading society for dermatological care, AADA takes every opportunity to weigh in on matters that impact our members and their patients.

[1] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/ipledge-risk-evaluation-and-mitigation-strategy-rems?utm_medium=email&utm_source=govdelivery
[2] https://www.aad.org/about-aad

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AADA is committed to the safe and responsible use of isotretinoin. Isotretinoin is used to treat recalcitrant nodular acne in non-pregnant patients, who are 12 years old or older with multiple inflammatory nodules with a diameter of 5 millimeters or greater. Through randomized double blinded studies, systemic isotretinoin therapy has been shown to be safe for patients with the appropriate medical supervision and incredibly effective at reducing acne and scarring. Isotretinoin is a mainstay of therapy for acne. The American Osteopathic College of Dermatology estimates over 2 million people have used isotretinoin.[3]

Isotretinoin is subject to a risk evaluation and mitigation strategy (REMS) managed through the iPLEDGE REMS program. The iPLEDGE REMS program goals are to manage to manage the risk of isotretinoin's teratogenicity, to minimize the risk of fetal exposure isotretinoin, and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions.[4] While AADA recognizes the absolute need to prevent fetal exposure, the administrative requirements for the complex iPLEDGE REMS program currently is associated with inadvertent harms that decrease access to isotretinoin and which promote healthcare disparities. Reduced access to appropriate treatment with isotretinoin can result in complications, such as increased psychosocial distress and adverse neuropsychiatric outcomes from poorly treated acne in addition to an increased risk of permanent scarring for the face and torso. There are also adverse financial impacts on patients and families due to the need for frequent appointments with increased co-pays, missed time at school or work, and transportation expenses. In addition, these requirements place tremendous administrative burden on clinical practices, resulting in opportunity costs that limit their capacity to care for patients where there is a shortage of dermatologists and long wait times.

AADA strongly urges FDA make additional changes to the program and continue to work with Isotretinoin Product Manufactures Group (IPMG) and other key stakeholders to ensure patients can safely access isotretinoin. FDA should require IPMG to make the following changes to the program:

- Reduce the monthly attestation requirements to yearly attestation for enrolled patients who cannot become pregnant.
- Remove the 19-day lockout period for patients who can become pregnant after the 7-day window because they do not effectively prevent fetal anomalies but instead create additional burdens for those who can become pregnant.
- Permit the use of FDA approved at-home pregnancy testing kits and telemedicine after the COVID-19 public health emergency.

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[3] https://www.aocd.org/page/Accutane#:~:text=Over%20two%20million%20people%20have,about%20its%20safety%20and%20effectiveness.

[4] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/ipledge-risk-evaluation-and-mitigation-strategy-rems?utm_medium=email&utm_source=govdelivery

- Restore key features of the iPLEDGE REMS platform, like the calendar function and enhanced enrollment.

Finally, AADA encourages FDA to continue to have transparent and continuous conversations with dermatologists and other impacted clinicians about any additional changes to the program.

I. FDA should reduce the attestation requirements for patients who cannot become pregnant.

In July 2022, IPMG shared they are reforming attestation requirements for individuals that cannot become pregnant from monthly to every 120 days, but to our knowledge this has not yet been approved and we have received no updates on the status of this reform from the IPMG or FDA. AADA applauds IPMG for recognizing the disruption in dermatological care caused by the monthly attestation requirement and that such onerous burdens can be time consuming and costly for patients. For those who cannot become pregnant, AADA proposes requiring qualification only at the time of enrollment and once yearly thereafter. Since the goal of the iPLEDGE REMS is to prevent fetal exposure to isotretinoin, there would be no additional risk introduced by this change.

AADA recognizes drug diversion is a significant concern for FDA and IPMG when administering the program. However, there is no evidence that such diversion exists for isotretinoin. AADA supports the goal of minimizing the risk of drug diversion using other strategies to accomplish this goal. For example, prescribers can limit the quantity of drugs supplied to a three-month supply or monthly with limited refills. In addition to being counseled about not sharing medication and not donating blood, patients could be counseled that sharing their medication will not help other acne patients because a complete course of isotretinoin, rather than a few pills, is needed for the medication to be effective. This change alone would be impactful because isotretinoin is prescribed more frequently to those who cannot become pregnant.

Furthermore, removing those who cannot get pregnant from the monthly attestation requirement in the iPLEDGE system would help decrease the multiple harms caused by the program, including documented health disparities in vulnerable populations, increased costs engendered by monthly attestations, and the use of higher doses of isotretinoin over a shorter period in a "race to the finish," which can cause more adverse effects of the medication.

AADA implores FDA to remove monthly attestation for individuals who cannot get pregnant and change this to annually.

II. FDA should remove the 19-day "lockout" period for missed initial window period to pick up the medication.

Often, at no fault of their own, many acne patients are "locked out" from starting isotretinoin due to missing the 7-day window to pick up their medication, due to insurance issues, medication availability and other factors. According to IPMG, the rationale for the 19-day "lockout" policy is based on a standardized 28-day ovulation cycle and the need to avoid starting drug in the "fertile period" in the second month. This policy fails to recognize that patients have already agreed to two forms of birth control, have two negative pregnancy tests 30 days apart, and are not further protected from pregnancy during that additional 19 days. Meanwhile, patients who are abstinent will have the same number of "fertile" cycles exposed to isotretinoin regardless of when they start the medication. Moreover, certain forms of contraception, such as combined oral hormonal contraceptive pills, Nexplanon, and some forms of long-acting reversible contraceptives (LARCs) suppress ovulation, and thus, patients do not have a "fertile period" after the initial 7 days of contraceptive use.

As an alternative, AADA proposes that physicians follow the same protocol for a missed window period that is in place for other months by requiring patients who can become pregnant that miss their 7-day window to have a second negative pregnancy test before going on isotretinoin. Although there may be a possibility patients will use isotretinoin during ovulation, patients that did not miss the window would also be on isotretinoin during ovulation.

Rather than penalizing the patients who missed the 7-day window, FDA and IPMG should ensure that they have extra screening by using an additional pregnancy test. Requiring a second negative pregnancy test for patients that missed their 7-day window would achieve the appropriate balance of avoiding fetal exposure to isotretinoin and ensuring patients have safe access to isotretinoin.

For the reasons stated above, AADA urges FDA to require IPMG remove the 19-day "lockout" period for missed initial window period to pick up the medication.

III. FDA should continue the use of at-home pregnancy tests and telemedicine following the end of the public health emergency.

While we acknowledge the risk of fetal anomalies from isotretinoin, AADA urges FDA and IPMG to consider more practical approaches for tracking pregnancy for those who use isotretinoin. During the COVID-19 Public Health Emergency (PHE), at-home pregnancy testing was permitted to satisfy the requirements of the iPLEDGE REMS program based on prescribers' best judgment, as consistent with FDA guidance at the outset of the PHE.[5] Throughout the PHE, FDA approved at-home pregnancy tests are safe and effective way to ensure patients are not pregnant every month.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-certain-rems-requirements-during-covid-19-public-health-emergency-guidance-industry-and.

Unfortunately, FDA indicated once the PHE is lifted, patients will be required to have their monthly pregnancy tests performed in a CLIA-certified lab. Reinstating the previous requirement of obtaining a pregnancy test from a CLIA-certified test in office or at a testing facility will only curtail access for people who can become pregnant. It can lead to an extra in person visit, which will delay enrollment and potentially increase the cost of medical care for isotretinoin patients. It can also lead to additional barriers to care, such as frequent travel to and from the doctor's office, additional time off from work, or unplanned childcare. Notably, iPLEDGE is the only REMS program to require pregnancy testing to be performed at a CLIA-certified lab, so removing this CLIA-certified lab requirement would better align the iPLEDGE program with other REMS programs for teratogenic medications.

AADA strongly recommends that FDA to permit FDA approved at-home pregnancy tests and telemedicine after the end of the PHE, tentatively scheduled to end on May 11, 2023.

IV. FDA and IPMG should restore key features and upgrades immediately, including calendar functionality, enhanced enrollment process, and general prescriber and designee updates.

AADA applauds FDA's and IPMG's efforts to modernize the program in 2021. For example, the inclusion of a gender-neutral categorization model for the iPLEDGE REMS program was a critical change to the program to address the needs of transgender or non-binary patients.

However, the iPLEDGE REMS system update in December 2021 led to numerous technical difficulties experienced by several physicians, patients, and pharmacists. For instance, problems with merging user data from the previous system into the new one prevented many users from logging into their iPLEDGE accounts, in some cases for several weeks, resulting in treatment disruptions for patients across the country.

Over the past year, AADA advocated for improvements to the iPLEDGE platform after its platform update, including restoring key features of the program that were removed when the program migrated to a new system. At a meeting in May 2022, IPMG shared that they are planning on upgrades including reinstating calendar functionality, enhancing the enrollment process, and general prescriber designee updates. AADA appreciates these improvements, but is frustrated that FDA must approve every upgrade, even small, common-sense improvements.

For instance, the lack of a calendar feature has caused confusion among health care providers and has resulted in delayed patient access to isotretinoin. When we raised this issue with IPMG last year, they mentioned that FDA must approve this change before it can reinstate this feature. Yet, AADA believes the calendar feature has already been approved by the FDA because it was a key feature before the transition to the new platform. AADA encourages FDA to clarify its approval of the calendar feature, or alternatively, immediately approve the reinstatement of the calendar feature.

Additionally, AADA members are also experiencing challenges with the platform's enrollment process. One member contacted IPMG to receive assistance and was informed the enrollment process can "take up to seven days" for IPMG to enter the patient. Our chief concern is that prescribers are not informed of when the patient has been successfully enrolled resulting in processing issues that delay scheduling follow-up visits, and thus, a patient's access to isotretinoin.

AADA strongly urges FDA to exercise its regulatory authority to encourage IPMG to make necessary updates to the iPLEDGE REMS system to ensure physicians can provide isotretinoin to their patients in a timely fashion.

V. AADA urges FDA to recognize the need to focus on health equity in the iPLEDGE REMS program.

AADA is concerned that the current iPLEDGE REMS program widens health disparities for patients of color, females, and Medicaid beneficiaries by limiting access for isotretinoin. The burdens of the iPLEDGE REMS program does lead clinicians and patients to use less optimal therapies but this effect is unequal – in addition to its obvious impact on persons who can become pregnant, there have been proven effects for patients with low socio-economic status, health literacy, and in rural locations. We urge FDA to heed these concerns and work with AADA and other stakeholders to promote health equity for patients with severe acne by removing unnecessary barriers to the iPLEDGE REMS program.

VI. AADA urges FDA and IPMG to remain transparent with key stakeholders to enhance the effectiveness of the iPLEDGE REMS program.

AADA greatly appreciates the ongoing dialogue between FDA and the public to ensure patients have access to life changing and medically necessary dermatological treatments. While we welcome impactful changes to the program, there is a need for transparent, open dialogue between key stakeholders, including IPMG, FDA, and prescribers. AADA has never been able to actually discuss concepts to improve the iPLEDGE REMS program. Instead, we interacted through "listening sessions" where we gave input to the IPMG and they then respond – often after prolonged delays and need for reminders – to any proposals, but often without explicit rational for their decisions. This approach is one-sided and shows no evidence of desire for collaboration with patients and prescribers in mind. For example, during the December 2021 iPLEDGE REMS system update, drug sponsors did not share any details of plans to change workflows in tandem with the technology platform change, nor did they seek dermatologists' or

other specialty clinicians' input into how their planned changes would impact access. As you know, this led to tremendous disruption of the program with a need for many subsequent meetings trying to solve problems that were created. A transparent process that includes input from multiple stakeholders and beta testing with prescribers, pharmacists, and patients when there are significant changes in the technologic workflows and upgrades would alleviate program users' frustration since their concerns would be identified and resolved before implementation of major changes to the platform.

In anticipation of potential future changes to the REMS program, AADA urges IPMG and FDA to hold regularly scheduled multi-stakeholder meetings so we may continue to collaborate on improvements to the program. We request greater transparency about the membership of the IPMG who currently remain nameless and faceless in all of our meetings with the exception of one designated spokesperson. We also request for a way to directly contact IPMG members rather than entirely via a generic group contact email.

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AADA is pleased with FDA's efforts to improve the iPLEDGE program to reduce unnecessary delays in acne care. On behalf of the American Academy of Dermatology's membership, representing dermatologist across the country, we strongly urge FDA and IPMG to make these necessary changes immediately to the iPLEDGE REMS Program. Thank you for your time and consideration. If you have any questions, please reach out to Stephanie Croney, Assistant Director of Regulatory Policy at scroney@aad.org.

Sincerely,

Mark Kaufmann, MD, FAAD

President

American Academy of Dermatology Association