June 3, 2022

Isotretinoin Products Manufacturers Group (IPMG)
Sent Via Email: ipledge@rems-pmo.com

Dear iPLEDGE REMS Program Sponsors:

On behalf of the nearly 16,500 U.S.-based members of the American Academy of Dermatology Association (AADA), I thank you for meeting with us on May 18, 2022 to discuss your planned changes to the iPLEDGE REMS system. We appreciate these efforts and urge IPMG to make these changes as quickly as possible.

We also appreciate IPMG listening to our proposed improvements to the program including removing the monthly attestation requirements for patients who cannot become pregnant and removing the 19-day lockout period for women who missed the 7-day window. We offer additional comments to address IPMG reservations with these proposed improvements and we welcome the opportunity to continue dialoguing with IPMG and FDA. **To that end, we again urge IPMG to hold regularly scheduled multi-stakeholder meetings so we may continue to collaborate on improvements to the program.**

Restore key features and upgrades immediately

As we discussed, throughout the crisis and after, the AADA has advocated for improvements to the iPLEDGE platform, including restoring key features that were removed when the program migrated (e.g., calendar functionality, enhanced enrollment process, and general prescriber and designee updates.) We appreciate IPMG listening to our concerns, and it is our understanding that necessary upgrades will be implemented. However, we are disappointed that IPMG was not able to provide a timetable for implementation, stating that the FDA must approve these changes first, which could take up to six months after submission, after which your vendor will need to time to implement within the iPLEDGE site.

CORRESPONDENCE
PO Box 1968
Des Plaines, IL 60017-1968
EMAIL: mrc@aad.org
WEB: aad.org

ROSEMONT, IL OFFICE
9500 W Bryn Mawr Avenue, Suite 500
Rosemont, IL 60018-5216
MAIN: (847) 330-0230
FAX: (847) 240-1859

WASHINGTON, DC OFFICE
1201 Pennsylvania Avenue, NW, Suite 540
Washington, DC 20004-2401
MAIN: (202) 842-3555
FAX: (202) 842-4355

We have heard from numerous members that the lack of a calendar feature has caused confusion and ultimately a delay in patient access to isotretinoin. As you can imagine, our patients have experienced significant obstacles already with accessing isotretinoin. Since the calendar feature has already been approved by the FDA as it was a key feature before the transition to the new platform, we fail to see any logical rationale that would prevent IPMG from implementing the restoration of the calendar immediately.

Our members have also lamented the platform's current enrollment process, and when they contact IPMG, the physician's office is informed that "it can take up to seven days for us to enter the patient." More troubling is that prescribers are not informed of when the patient has been enrolled. These processing issues delay scheduling follow-up visits and thus a patient's access to isotretinoin, and we urge IPMG to implement their planned upgrades immediately. Should IPMG believe that the FDA review is required, then we urge IPMG to request that FDA expedite its review so IPMG may make these upgrades expeditiously.

Proposed structural changes to the iPLEDGE REMS program

As we discussed during our conversation, there remain several concerns with the iPLEDGE REMS program that cause burdens to prescribers and limit patient access to isotretinoin. Of greatest concern are the monthly attestation requirements for patients who cannot become pregnant and the 19-day lockout period for patients who can become pregnant after the 7-day window for filling their prescription has expired. While we recognize that IPMG has reservations with our proposed modifications, we would like to continue to discuss these important reforms with the central tenet of achieving the appropriate balances of limiting the risk of fetal exposure to isotretinoin while at the same time providing patients with safe access to isotretinoin.

Remove monthly attestation requirements for patients who cannot become pregnant

As we shared, instead of requiring patients be qualified monthly to receive isotretinoin, we propose 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. During our call, IPMG representative Greg Wedin expressed a concern that removing the monthly attestation would increase the potential for drug diversion. While there is little to no evidence that such diversion actually exists, the 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 one-month supply and avoid authorizing automatic 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 since a whole course of isotretinoin rather than a few pills is needed for the medication to be effective. This change alone would be hugely impactful as

isotretinoin is prescribed more frequently to those who cannot become pregnant. Removing them from monthly attestation in the iPLEDGE system would help decrease the multiple harms caused by the iPLEDGE REMS 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 of time in a "race to the finish" which can cause more adverse effects of the medication. We would welcome the chance, via multi-stakeholder meetings, to identify additional solutions or approaches.

During our conversation, Mr. Wedin also mentioned a concern about making too many changes to the REMS program thereby causing more problems. This proposal is not new. The AADA iPLEDGE workgroup published proposed changes to the program in 2019 and published this proposal in JAMA Dermatology (See attached article). At that time, we reached out to the IPMG, but the proposal was never considered. With respect to the concern raised, we do NOT think the problems with transition to a new platform justifies delaying implementation. This change is supported by AADA and our members who would eagerly welcome this change! A transparent process that includes input from multiple stakeholders would alleviate program users' frustration since their concerns would be identified and resolved before implementation.

Remove the 19-day "lockout" period for missed initial window period to pick up the medication

Often no fault of their own, many patients are "locked out" from starting isotretinoin due to missing the 7-day window. During our most recent call, IPMG shared that 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 that second month. However, common forms of contraception (i.e., combined oral contraceptive pills, Nexplanon) suppress ovulation and therefore patients do not have a "fertile period" after the initial 7 days of contraceptive use. (Withdrawal bleeding on oral contraceptives is not due to ovulation.) 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 on abstinence will have the same number of "fertile" cycles exposed to isotretinoin regardless of when they start.

Our proposed solution is to follow the same protocol for a missed window period that is in place for other months by requiring patients able to get pregnant that miss their 7-day window to have a second negative pregnancy test before going on isotretinoin. While the concern may be that these patients will be on isotretinoin during ovulation, we remind IPMG that patients that did not miss the window would also be on isotretinoin during ovulation. Our proposal, rather than penalizing the patients who missed the 7-day window, would ensure that they have more

screening through an additional pregnancy test. Therefore, 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.

We request a meeting to discuss this issue further and to invite colleagues from the American College of Obstetrics and Gynecology (ACOG) to weigh in on the utility of the 19-day waiting period requirement from a reproductive standpoint.

Focus on health equity
Moreover, on our call we presented several facts that demonstrated that the current iPLEDGE REMS program may create health disparities for patients of color, women, and individuals on Medicaid by limiting access for isotretinoin. We urge IPMG to take these concerns seriously and work with AADA to promote health equity for patients with severe acne by removing unnecessary barriers to the iPLEDGE REMS program.

Increase transparency
We reiterate the need for transparent, open dialogue between key stakeholders including IPMG, FDA, and prescribers. To improve cooperation with the physician community we again request that a board-certified dermatologist representative be added to IPMG.

Transparency also means sharing data and information, and we request responses to the following questions:

- Since our discussion, do you have better understanding of a timeline on the implementation of the improvements to the platform?
- What is the percentage of users of iPLEDGE REMs in the unable to get pregnant category?
- To facilitate better cooperation between AADA and IPMG, can you provide a contact name, phone number and email address for AADA's use?
- Clarify if the patient counseling form will be available online?

Only through collaborative discussions can the iPLEDGE REMS program achieve necessary balance of preventing the risk of fetal exposure and ensuring reliable, safe patient access to isotretinoin.

To that end, we suggest that we meet again either on Thursday, June 16, 2022 at 4:00 PM ET or on Thursday, July 7, 2022 at 4:00 PM ET. To schedule a time that works for IPMG, and to provide a timely response to our questions, please contact AADA's Director of Public Policy and Healthcare Economics Chad Appel, JD at Cappel@aad.org. We look forward to speaking with you again soon.

Sincerely,

Bruce Brod, MD, MHCI, FAAD
Chair, Council on Government Affairs and Health Policy
American Academy of Dermatology Association

CC:

Robert M. Califf, MD, Commissioner, FDA
Mark Kaufmann, MD, FAAD, President, AADA
Ilona Frieden, MD, FAAD, Chair, PLEDGE Workgroup, AADA
John Barbieri, MD, FAAD, Member, iPLEDGE Workgroup, AADA
Andrea Zaenglein, MD, FAAD, Member, iPLEDGE Workgroup, AADA