May 2, 2023

Patrizia Cavazzoni, MD
Director, Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
25 New Hampshire Avenue
Silver Spring, Maryland 20903

Submitted electronically to Patrizia.Cavazzoni@fda.hhs.gov

Dear Dr. Cavazzoni,

On behalf of the nearly 16,500 U.S.-based members of the American Academy of Dermatology Association (AADA), I write this letter *to request* a meeting with the Food and Drug Administration (FDA) to discuss the AADA's on-going concerns with the iPLEDGE REMS program and the lack of consistent and transparent communication from the Isotretinoin Productive Manufacturers Group (IPMG) with our members.

I want to express our gratitude to Food and Drug Administration (FDA) staff for hosting a meeting with the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee (Advisory Committees) to discuss potential changes to the iPLEDGE Risk Mitigation and Evaluation Strategy (REMS) requirements in order to "minimize the existing burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin oral capsules from patients."[1] The meeting allowed for a meaningful discussion between Advisory Committee members, IPMG representatives, FDA staff, and the public.

[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

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

The AADA writes this letter to outline our on-going concerns with the iPLEDGE REMS program and *to request a meeting* with FDA staff to discuss the Advisory Committees' recommendations.

Support Recommendation to Remove the Monthly Attestation Requirement for Individuals Who Cannot Become Pregnant.

The Advisory Committees' recommendations will improve safe access to isotretinoin and aid IPMG in making the needed updates to the program. The AADA strongly urges FDA to quickly adopt the committees' recommendations and we request a meeting with CDER staff to discuss our on-going concerns with the iPLEDGE REMS program.

The AADA applauds the committees' recommendation to reduce the monthly attestation for patients who cannot become pregnant to *at least* 120 days with the majority of committee members supporting an interval of six months or only at time of enrollment. However, based on IPMG's response to the committee questions, it is unclear whether patients who cannot become pregnant would still be required to have monthly medical visits with a certified prescriber, either in-person or via telehealth. The AADA explicitly rejects any proposal that would require patients who cannot become pregnant to have monthly in-person medical visits, as dermatologists can safely monitor these patients for six months or longer. Therefore, we strongly recommend that any reduction in monthly attestation is associated with similar reductions in the frequency of required counseling and the allowance of time-limited refills. Without these changes, patients will still need monthly visits for counseling and/or to obtain prescriptions, which will negate any potential benefits from the reduction in attestation requirements.

Additional monthly visits for this patient population are medically unnecessary. They create additional burdens for patients and will not improve access to isotretinoin or reduce heath disparities in dermatological care. Instead, monthly counseling visits result in long wait times, high cost for patients, and limited appointments, particularly for rural and low-income patients. The AADA agrees that counseling patients about the dangers of sharing isotretinoin and donating blood while on the medication is vital for the safety of our member's patients; however, such counseling does not have to occur monthly for this patient population. Physicians can effectively monitor patients who cannot become pregnant in six-month intervals or greater, especially for patients on stable dosages and improving on the medication. Moreover, as

suggested by some advisory committee members, there are other effective ways to counsel patients on the dangers of fetal exposure, sharing isotretinoin, and donating blood while on the medication. For instance, pharmacies can provide counseling while dispensing medication or the manufacturers can create an interactive, age-appropriate online module that patients can complete remotely. Additionally, text messages and automated emails from the iPLEDGE program could be used to send timely reminders to patients about the risks associated with isotretinoin. As an added benefit, this approach might also lead to more standardized counseling.

Accordingly, the AADA rejects the need for monthly medical visits for patients who cannot become pregnant. We encourage FDA to reduce monthly counseling visits to 6 months or longer as the committee recommended and to consider sensible alternatives to monthly counseling.

Support Recommendation to Remove the 19-day Lockout Period for Individuals Who Can Become Pregnant

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. Even the OB/GYN Consultant hired by IPMG noted that the 19-Day Lockout period is not based on biology or clinical evidence, but rather a precautionary measure put in place by IPMG. Patients who complete an additional pregnancy test after a window period have been *more* intensively screened than those who do not. In addition, since a 5- to 8-month course of continuous therapy is typically required, it does not matter when in the menstrual cycle the drug is started, as an ovulating patient will experience the same number of "fertile periods" on therapy no matter when in the menstrual cycle they start the medication (i.e. calendar thought experiment).

Often, 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 related to social determinants of health. 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.

The AADA recommends that FDA extend the 7-day prescription window to 10-days to account for events outside the patient's control (e.g. insurance approval delays), and to eliminate the 19-day lockout period for missed prescription windows. For a missed initial prescription window, the patient could immediately repeat a pregnancy test to start a new prescription window period, similar to what is done in every other month of treatment. Finally, timing of pregnancy testing should not be based on menstrual cycles as this is not biologically rational for many patients who might not be ovulating due to contraception choices or medical comorbidities.

Support Recommendation to Increase Transparency between IPMG and AADA and add a Practicing Dermatologist to the IPMG.

As mentioned by several advisory committee members, there is a need for transparent, open dialogue between key stakeholders, including IPMG, FDA, and prescribers. It was notable that not a single dermatologist spoke on behalf of the IPMG during their presentation. Prior to the joint advisory meeting, the AADA was unable engage in meaningful dialogue with IPMG to discuss proposals to improve the iPLEDGE REMS program. Additionally, when significant changes were made to the platform by IPMG, drug sponsors did not share any details of plans to change workflows or the platform, nor did they seek dermatologists' or other specialty clinicians' input into how their proposed changes would impact patient access to isotretinoin.

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 because their concerns would be identified and resolved before implementation of major changes to the platform. We encourage IPMG to allow a dermatologist, preferably one selected by AADA, to regularly attend stakeholder meetings with FDA, drug manufactures, or other key stakeholders.

Furthermore, over 200 AADA members have shared their concerns with iPLEDGE and the lack of transparent communication from IPMG. For example, an AADA member was in communication with IPMG for several months to rectify a compliance issue. Despite her numerous attempts to

share the required paperwork and meet any additional requests, she was punitively deactivated from the program for a clerical error with little no recourse for a decision made by IPMG. Issues like this can be resolved by having a consistent and responsive point of contact for prescribers' compliance questions or appeals with IPMG and have a dermatologist as a member of IPMG.

The AADA fervently believes that only through collaborative discussions can the iPLEDGE REMS program achieve necessary balance of mitigating the risk of fetal exposure and ensuring reliable, safe patient access to isotretinoin. ***We strongly advocate for continued and transparent communication between IPMG and dermatologists, including identifying a consistent point of contact for prescriber grievances and compliance issues***.

Thank you again for allowing the public to provide input on future changes to iPLEDGE. Should you need additional information or to schedule a meeting, please contact AADA's Assistant Director for Regulatory Policy Stephanie Croney, JD at scroney@aad.org. We appreciate your consideration of our request.

Sincerely,

Terrence A. Cronin Jr. MD FAAD

Terrence A. Cronin Jr., MD, FAAD
President

CC:

Cynthia LaCivita, PharmD, Director, Division of Risk Management, Food and Drug Administration