U.S. FOOD & DRUG ADMINISTRATION

SCIENTIFIC WORKSHOP ON

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

SUMMARY REPORT

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Introduction

Erythropoietic protoporphyria (EPP), the third most common porphyria, is a group of genetic disorders that is characterized by photosensitivity that often manifests as severe pain, swelling and/or burning. There is no FDA-approved treatment for EPP. Treatment for EPP has primarily focused on minimizing sun exposure, while other treatments may include dietary management, over-the-counter and prescription sunscreen and phototherapy.

On October 24, 2016, FDA held a scientific workshop on EPP to discuss how best to facilitate and expedite the development of safe and effective drug therapies to treat signs and symptoms related to EPP. The discussion at the workshop was dedicated to two main topics: (1) patient perspectives on EPP symptoms, daily impacts and approaches to treatment, and (2) scientific discussion of EPP and challenges in clinical trial design. Approximately 105 patients and caregivers attended the meeting in-person, and an additional 30 patients and caregivers participated through the live webcast. Patient participants represented a range of diversity in age (including pediatric participants), sex, and length of time since EPP diagnosis. Although workshop participants may not fully represent the diverse population living with EPP, the input reflected a range of experiences with EPP symptoms and treatments. In addition to patient and caregiver participants, approximately 55 other stakeholder participants, including regulators, healthcare providers, researchers and medical product developers, also attended the meeting in person.

The workshop began with presentations from scientific experts on the epidemiology and natural history of EPP and current approaches to treatment. Following the presentations, the morning discussion focused on obtaining perspectives from patients and caregivers on symptoms, daily impacts and current approaches to treatment. This discussion was kicked off by a panel of patients, followed by a semi-structured, large-group facilitated discussion with patients and caregivers in the audience and on the webcast. In the afternoon, FDA presented an overview of the FDA regulatory process. An expert then presented on the challenges in clinical trial design for EPP, followed by a panel discussion with experts on specific trial considerations and challenges. Patients and caregivers in the audience were also invited to participate and engage in the dialogue during the afternoon session. To supplement the input gathered at the workshop, EPP patients and others were encouraged to submit comments to a public docket[1], which was open until December 24, 2016. Thirty-two comments were submitted to the public docket, the majority by individual patients and caregivers.

This report summarizes the input shared by participants during the meeting, through the webcast and through the public docket. To the extent possible, the terms used in this report to describe specific EPP symptoms, impacts, and treatment experiences reflect the words used by in-person participants, web participants, or public docket commenters. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of EPP that are not included in this report. More information, including the archived webcast and meeting transcript, is available on the meeting website: https://www.fda.gov/Drugs/NewsEvents/ucm501389.htm.

1. A docket is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

Overview of Erythropoietic Protoporphyria

Dr. Henry Lim from the Henry Ford Hospital began the presentations with an overview of the epidemiology and natural history of EPP. Dr. Lim also explained the pathophysiology of EPP, and presented information about the prevalence of EPP, clinical symptoms and manifestations. He concluded with information on emphasizing the burden of having EPP on quality of life.

The second presentation by Dr. Joyce Teng from the Stanford University School of Medicine addressed current approaches to treatment and challenges. Dr. Teng highlighted that there are no FDA approved treatments for EPP or specific treatments for acute photosensitivity. She provided an overview of current management approaches, including diagnostic screening, monitoring, protective clothing and other lifestyle changes, cholestyramine and other porphyrin absorbents, plasmapheresis and intravenous hemin and transplantation. Dr. Teng also briefly discussed supportive treatments such as analgesics, and then concluded her presentation by presenting on potential therapies including beta-carotene, phototherapy, afamelanotide, cimetidine and hematopoietic cell transplantation. For each of the potential therapies, Dr. Teng provided an overview of the current science and data available, limitations of the potential therapy, and possible next steps for drug development.

Morning Session: Patient-Focused Discussion of Symptoms and Current Approaches to Treatment

A panel of patients shared perspectives on the range of EPP symptoms, daily impacts and current approaches to treatment. The panelists included two pediatric patients, ages 11 and 16, and three adult patients. Panel comments were followed by a semi-structured large-group facilitated discussion that encouraged participation from other patients and caregivers in the audience and on the webcast. The discussion was led by an FDA facilitator, and included a panel of FDA reviewers who listened throughout the session and asked follow-up questions.

The patient input from the workshop and the docket comments underscore the chronic and debilitating effect that EPP has on patients' lives and their loved ones, as well as the diverse experiences of patients with EPP, and the challenges they face in finding effective therapies to manage their condition. Several key themes emerged from this workshop:

- **EPP is a chronic condition with debilitating symptoms including burning, stinging, itching and pain.** Participants described the burning and stinging as a symptom that initially manifests as "tingling". Once the tingling manifests, participants expressed that this was an indicator that they were exposed to light too long and a phototoxic "reaction" would follow. Participants indicated that reactions typically manifested as pain. The pain was described as being under the skin and often chronic. A few participants, particularly in the pediatric population, described that the tolerance for pain for people living with EPP is very high. For example, participants reported that they may have a broken bone, but not even realize it.
- **Symptoms and manifestations of EPP are unpredictable.** Participants described their reactions to light exposure as unpredictable. Reactions could be triggered by a range of factors, including length of light exposure (ranging from seconds to a few hours), changes in temperature, and weather conditions. Participants also described how their photosensitivity reacted to sunlight, as well as other forms of light, such as television screens, reflection of light from snow, and indoor fluorescent lights.

- **EPP patients experience a wide range of severity in reactions to light exposure.** Participants described a range of severity for reactions to light exposure, for which level and duration of pain were highly variable. Some participants described reactions that lasted hours. Others experienced reactions for days and some for months. Participants also stressed that precautions taken prior to light exposure or during light exposure may greatly impact the duration of the reaction. Some participants also discussed how their reactions have affected their cognitive abilities, such as their ability to think clearly and their memory.
- **EPP affects all aspects of patients' lives.** Participants stated that EPP caused them and their loved ones to limit or completely stop participating in activities, such as family trips and sports, leading to social isolation. Participants also shared the significant impact of EPP on their emotional well-being. They particularly highlighted the impact of anxiety, and the fear of going outside on their daily lives. Participants also commented on the destructive impact of EPP on multiple generations of their families.
- **There is an unmet medical need in the treatment and management of EPP.** Participants shared their experiences with prescription medicines and phototherapy, as well as non-drug therapies including protective clothing. Participants highlighted the varying degrees of success in managing their symptoms with these therapies, and focused on the downsides of these treatments. Several participants stated that afamelanotide[2] was a part of their treatment regimen. Some participants discussed not having a reaction at all during their time on afamelanotide. Others mentioned that the drug increased the amount of time that he or she could spend exposed to light before experiencing a reaction. A few participants also described reactions that were less severe while on afamelanotide, including both the level of pain and how the long the pain lasted.
- **The EPP patient community raised issues regarding drug development.** Participants expressed the need for medications that were effective in delaying the onset of their reactions therefore allowing them more time to do activities that are important to them. Participants also expressed decreased severity of reactions as a clinically meaningful outcome.

FDA recognizes that patients have a unique ability to contribute to our understanding of the broader context of this condition, which is important to our role, and that of others, in the drug development process. The patient input generated through this workshop strengthens FDA's understanding of the burden of EPP on patients and the treatments currently used to treat EPP and its symptoms. FDA staff could consider this input during the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval.

2. Afamelanotide is not currently approved for marketing in the United States.

Afternoon Session: Scientific Discussion on Challenges in Clinical Trial Design

The focus of the afternoon scientific discussion was drug development and identifying important issues in drug development for EPP that can help researchers, drug developers, patient communities and FDA understand how best to advise, support, conduct and evaluate drug development efforts and programs.

Overview of FDA Regulatory Process

Paul Phillips, a Regulatory Project Manager in the Division of Dermatology and Dental Products within FDA's Center for Drug Evaluation and Research (CDER), kicked off the afternoon session of the workshop with an overview of drug development and the FDA regulatory process. He described the drug development process, from the discovery phase to the post-marketing phase, highlighting FDA's role at each stage in the development. Following Mr. Phillips' presentation, Dr. Kathryn O'Connell, a medical officer in CDER's Office of New Drugs Rare Diseases Program, examined considerations for rare disease drug development and review. Dr. O'Connell provided an overview of the Orphan Drug Act[3], the need to demonstrate safety and efficacy, the relevant statutory standards and explored endpoints in clinical trials, defining them according to statute. She concluded with a brief discussion on the standard and accelerated approval pathways at FDA and the expanded access program.

Challenges in Clinical Trial Design for EPP

Dr. Elisabeth Minder, from Stadtspital Triemli, Porphyria Outpatient Clinics in Switzerland, presented on the challenges in clinical trial design for EPP. Dr. Minder described the complexity of EPP that negatively affects outcomes measurements, the high variability of symptoms which reduces statistical significance, and the adaptation due to early onset in life which leads to an overestimation of quality of life before an effective treatment. She also noted that if there is no preexisting effective treatment it may be difficult to validate an outcome instrument. Additional clinical trial design challenges expressed by Dr. Minder included, determining a standard definition of EPP which is applicable across patient populations, pre-determining treatment rationale, and lack of ability to consistently apply evidence-based medicine decisions due to lack of research.

Following the presentation, experts were asked to participate in dialogue on drug development for EPP and patients and caregivers in the audience were also invited to participate. The following key themes emerged:

- Patients want to be as active as possible in the work to develop and evaluate new treatments. Approximately half of the patient participants indicated having participated in a clinical trial for EPP in the past. About three-fourths of the patient participants indicated that he or she would be willing to consider participating in a clinical trial for EPP in the future. Patient participants' main considerations for clinical trial participation included the location of the study site, concerns about side effects, and the complexity of the study requirements.

3. To learn more about the Orphan Drug Act, please visit: https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/ucm364750.htm

- Experts discussed the need for further natural history studies and tools to better define EPP and the patient population, in order to better understand the underlying cause for the variability between patients. Experts also discussed the benefits of stratifying the patient population based on pathology such as the amount of the reduction in biotransformation of protoporphyrin into heme or the underlying genetic mutation in an effort to explore targeted therapies in addition to broad treatments for symptomatic and clinical improvement.
- Experts identified choosing endpoints that are meaningful to patients and can be reliably measured and interpreted as the most significant factor to consider in designing a robust and feasible clinical trial. Experts discussed sunlight exposure and pain intensity as possible complementary endpoints, considering that if only one aspect is measured, and not the other, the outcome measurement loses sensitivity. Experts also discussed the potential and limitation of using total number of hours of sun exposure without pain as an endpoint.
- Experts stressed the need for patient-reported outcome (PRO) measures. Patients at the workshop expressed their ability to spend more time in the sun as a meaningful benefit, and so experts proposed pain-free sun exposure as a possible PRO. An expert added that since measuring pain is unreliable and inconsistent in terms of the result, a PRO would be the best measure.
- Experts discussed measuring benefit to patients in terms of activities that reflect the quality of life gained, such as being able to walk to the mailbox, or being able to drive to work, rather than in terms of number of minutes of sun exposure gained. Experts noted that benefits need to be measured in a systematic way in order to be able to demonstrate efficacy.
- Experts discussed the use of photoprovocation testing in clinical trials, and acknowledged the potential limitation that photoprovocation can be too variable and yield an elevated baseline. In addition, it was noted that photoprovocation does not allow for objective measurement and that reproducibility would be an issue.
- Experts discussed extrapolating efficacy data from adults to children. During the discussion, experts highlighted the need for good quality of life indicators in the pediatric population.

Conclusion

As described in this report, this workshop emphasized the need for increased research and available treatments for EPP. Through this workshop, FDA learned more about what matters most to patients and caregivers regarding symptoms, impacts, and aspects of EPP treatments. The participants' sense of community and their desire to advocate for current and future generations at risk for EPP were strikingly clear. The scientific component of the workshop allowed FDA to obtain expert input on the complex issues surrounding drug development and treatment of EPP more broadly, including clinical trial design and conduct. It is clear that EPP has a debilitating physical, social and emotional impact on the lives of patients and their loved ones. FDA shares the patient and healthcare community's desire and commitment to furthering the development of new safe and effective drug therapies to treat or prevent EPP.

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