4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-N-0567]

Notice of Decision Not to Designate Pneumocystis Pneumonia as a Tropical Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency), in response to suggestions submitted to Docket No. FDA-2008-N-0567, has analyzed whether *Pneumocystis* pneumonia (PCP) meets the statutory criteria for designation as a tropical disease for the purposes of obtaining a priority review voucher (PRV) under the Federal Food, Drug, and Cosmetic Act (FD&C Act), namely whether it primarily affects poor and marginalized populations and whether there is "no significant market" for drugs that prevent or treat PCP in developed countries. The Agency has determined that PCP does not meet the statutory criteria for designation as a tropical disease and declines to designate it as such.

DATES: [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: Submit electronic comments on additional diseases suggested for designation to https://www.regulations.gov. Submit written comments on additional diseases suggested for designation to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

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Rm. 6242, Silver Spring, MD 20993-0002, 301-796-1300, Katherine.Schumann@fda.hhs.gov; or Office of Communication, Outreach and Development (OCOD), Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

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I. Background: Priority Review Voucher Program

Section 524 of the FD&C Act (21 U.S.C. 360n), which was added by section 1102 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), uses a PRV incentive to encourage the development of new drugs, including biologics, for prevention and treatment of certain diseases that, in the aggregate, affect millions of people throughout the world. Further information about the tropical disease PRV program can be found in guidance for industry "Tropical Disease Priority Review Vouchers" (81 FR 69537, October 6, 2016, available at https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic). Additions to the

statutory list of tropical diseases published in the *Federal Register* can be accessed at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm.

In August 2015, FDA published a final order (80 FR 50559, August 20, 2015) (final order) designating Chagas disease and neurocysticercosis as tropical diseases. That final order also sets forth FDA's interpretation of the statutory criteria for tropical disease designation and expands the list of tropical diseases under section 524(a)(3)(R) of the FD&C Act, which authorizes the FDA to designate by order "[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations" as a tropical disease.

FDA has applied its August 2015 criteria as set forth in the final order to analyze whether PCP meets the statutory criteria for addition to the tropical disease list. As discussed below, the Agency has determined that PCP does not meet the statutory criteria for designation as a "tropical disease" and thus will not add it to the list of tropical diseases whose applications may be eligible for a priority review voucher.

II. Decision Not to Designate Pneumocystis Pneumonia

FDA has considered all diseases submitted to the public docket (FDA-2008-N-0567) between August 20, 2015, and June 20, 2018, as potential additions to the list of tropical diseases under section 524 of the FD&C Act, under the docket review process explained on the Agency's website (see https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm). Based on an assessment using the criteria from its final order, FDA has

determined that PCP will not be designated as a "tropical disease" under section 524 of the FD&C Act.

Pneumocystis species are genetically distinct, host-specific opportunistic fungal pathogens widely found in nature. *Pneumocystis jirovecii*, found in humans, causes PCP in immunocompromised patients. Human immunodeficiency virus (HIV)-infected patients with a low CD4 count are at the highest risk of PCP. Others at substantial risk include hematopoietic cell and solid organ transplant recipients, those with cancer (particularly hematologic malignancies), and those receiving glucocorticoids, chemotherapeutic agents, and other immunosuppressive medications. Among patients with acquired immunodeficiency syndrome (AIDS) and PCP, the mortality rate is 10 to 20 percent during the initial infection, but the rate increases substantially when the patient requires mechanical ventilation. The mortality rate among patients with PCP in the absence of AIDS is 30 to 60 percent, depending on the population at risk, with a greater risk of death among patients with cancer than among patients undergoing transplantation or those with connective tissue disease (Ref. 1).

A. Significant Market in Developed Nations

In developed nations, a sizable market exists for PCP prophylaxis drugs. The prevalence of stage-3 AIDS by year end 2014 in the United States (i.e., with AIDS requiring PCP prophylaxis) was approximately 530,000 (Ref 2). In addition, approximately 30,000 solid organ transplantations (Ref. 3) and 19,000 hematopoietic stem cell transplants (Ref. 4) are performed annually in the United States. These patients receive PCP prophylaxis for 6 months to one year in the post-transplantation period. There were also about 6,590 new cases of acute lymphocytic leukemia (ALL) eligible for PCP prophylaxis in the United States in 2016 (Ref. 5).

Regarding treatment of PCP, the incidence of PCP has declined substantially with widespread use of PCP prophylaxis and anti-retroviral therapy (ART) (see, e.g., Refs. 6-9). In a prospective cohort study of 8070 participants at 12 HIV clinics across the United States, the incidence in 2003-2007 was <1 case per 100 person-years (Ref. 10). PCP now mainly occurs in individuals who are unaware that they are HIV positive, lack access to medical care, or are noncompliant with medications.

In contrast to HIV-positive patients, the incidence of PCP in non-HIV patients is rising in some areas (see, e.g., Refs. 8, 9, 11); however, the number of cases in non-HIV patients is still below the number of cases in HIV-positive patients (Ref. 12). In the United States, the incidence of PCP is estimated to be 9 percent among hospitalized HIV/AIDS patients and 1 percent among solid organ transplant recipients (Ref. 13).

Current clinical guidelines recommend chemoprophylaxis against primary PCP for HIV infected persons with a CD4 cell count <200 cells/µL or a history of oral candidiasis (Ref. 14). As indicated above, the prevalence of stage-3 HIV infection (i.e., AIDS requiring PCP prophylaxis) by year end 2014 in the United States was approximately 530,000 patients, including 18,303 patients diagnosed with stage-3 HIV infection in 2015 (Ref. 2). These subjects were eligible for PCP prophylaxis.

In summary, a sizable market in developed nations exists for drugs indicated for prevention of PCP. At present, FDA is unaware of any significant funding by military, the Biomedical Advanced Research and Development Authority (BARDA), or any other United States Government sources for drug development targeting treatment of or prophylaxis against PCP.

B. Disproportionately Affects Poor and Marginalized Populations

Although no disability-adjusted life year (DALY) data were found to distinguish the disease burden of PCP in developing versus developed countries, it is noted that PCP occurs frequently among HIV-infected patients in many parts of the developing world. In addition, the prevalence of HIV-infected persons with PCP ranges from 24 percent (42/177) in Mexico (Ref. 15) to 55 percent in Thailand (Ref. 16). A Brazilian study found 55 percent (15/27) of HIV-infected persons with respiratory symptoms had PCP (Ref. 17).

Studies estimating the burden of fungal infections in different countries suggest low total yearly number of PCP cases in Belgium (n = 120), in contrast, for example, to 9,600 cases among HIV-infected people in Tanzania in 2012 (Refs. 18 and 19). In Uganda, the frequency of PCP among HIV-infected patients hospitalized with suspected pneumonia who had negative sputum acid-fast bacilli smears and underwent bronchoscopy decreased from nearly 40 percent of bronchoscopies between 1999 and 2000 to less than ten percent between 2007 and 2008 (Ref. 20). However, it is estimated that there are approximately 800 HIV-positive adults with PCP annually and up to 42,000 children with PCP annually in Uganda (Ref. 21). In Vietnam, the prevalence of PCP was 608 cases in 2012, 1149 cases per year in Senegal and 990 cases yearly in Nepal (HIV positive individuals) (Refs. 22, 23, 24). In Ukraine, 13.5 per 100,000 individuals develop PCP annually (Ref. 25).

High rates of anti-*Pneumocystis* antibodies among African children suggest that exposure to the organism is common, and that *Pneumocystis jirovecii* is a common cause of pneumonia among children in sub-Saharan Africa (Ref. 26). Furthermore, limited diagnostic resources and less commonly performed induced sputum and bronchoalveolar lavage with reliance on empiric

therapy may cause underestimation of the true incidence of PCP (Ref. 27). Several studies suggest that the incidence of PCP is increasing in Africa (Refs. 26, 28, 29).

PCP has been reported to be a leading cause of death in HIV-infected infants, responsible for at least one quarter of all pneumonia deaths in HIV-infected infants (Ref. 30). A recent review found PCP to be one of the factors strongly associated with mortality from acute lower respiratory infections in children under five years of age in low-income economies, lower-middle-income economies, and upper-middle-income economies (referred to as low- and middle-income countries (LMICs)), with odds ratio of 95 percent confidence interval of 4.79, 2.67-8.61 (Ref. 31). However, the incidence of PCP in infants and children in developed countries has decreased because PCP prophylaxis has been initiated in all neonates born to HIV-positive mothers (Refs. 32 and 33).

The HIV epidemic imposes a particular burden on women and children, specifically in sub-Saharan Africa where women account for approximately 57 percent of all people living with HIV (Ref. 34). In 2012, there were an estimated 260,000 newly infected children in LMICs (id.). Children with HIV are more likely to face gaps in access to HIV treatment. In 2012, approximately 34 percent of children had access to HIV treatment versus approximately 64 percent for adults (id.). Since PCP is the most prevalent in persons infected with HIV (Ref. 1) and HIV disproportionately impacts women and children, it is reasonable to conclude that PCP also disproportionately affects these populations.

PCP has not been designated by the World Health Organization (WHO) as a neglected tropical disease (Ref. 35).

C. FDA Determination

In sum, although PCP disproportionately affects poor and marginalized populations, it is an infectious disease for which there is a significant market in developed nations for drugs indicated for prevention of PCP. Based on the information reviewed, FDA has determined that PCP does not meet the statutory criteria for a tropical disease in section 524 of the FD&C Act.

III. Process for Requesting Additional Diseases to be Added to the List

FDA's current determination regarding PCP does not preclude interested persons from requesting its consideration in the future. To facilitate the consideration of future additions to the list, FDA established a public docket (see https://www.regulations.gov, Docket No. FDA-2008-N-0567) through which interested persons may submit requests for additional diseases to be added to the list. Such requests should be accompanied by information to document that the disease meets the criteria set forth in section 524(a)(3)(S) of the FD&C Act. FDA will periodically review these requests, and, when appropriate, expand the list. For further information, see https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm.

IV. Paperwork Reduction Act

This notice reiterates the "open" status of the previously established public docket through which interested persons may submit requests for additional diseases to be added to the list of tropical diseases that FDA has found to meet the criteria in section 524(a)(3)(S) of the FD&C Act. Such a request for information is exempt from Office of Management and Budget review under 5 CFR 1320.3(h)(4) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). Specifically, "[f]acts or opinions submitted in response to general solicitations of

comments from the public, published in the *Federal Register* or other publications, regardless of the form or format thereof" are exempt, "provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency's full consideration of the comment."

V. References

The following references have been placed on display at the Dockets Management Staff (see ADDRESSES). They may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday and are available electronically at https://www.regulations.gov. (FDA has verified the website addresses, but FDA is not responsible for any subsequent changes to the websites after this document publishes in the *Federal Register*.)

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Dated: August 21, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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