CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

[Docket No. CPSC–2021–0027]

Poison Prevention Packaging Requirements; Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More Than 80 mg of the Drug

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The Consumer Product Safety Commission (Commission or CPSC) is amending the child-resistant packaging requirements of CPSC's regulation to exempt baloxavir marboxil tablets, currently marketed as XOFLUZA™, in packages containing not more than 80 mg of the drug, from the special packaging requirements. XOFLUZA is used to treat the flu, and the drug is taken in one dose within 48 hours of experiencing flu symptoms. The final rule exempts this prescription drug product on the basis that child-resistant packaging is not needed to protect young children from serious injury or illness because the product is not acutely toxic and lacks adverse human experience associated with ingestion.

DATES: The rule is effective May 20, 2024.

FOR FURTHER INFORMATION CONTACT: Will Cusey, Small Business Ombudsman, U.S. Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504–7945 or (888) 531–9070; email: *sbo@cpsc.gov.*

SUPPLEMENTARY INFORMATION:

A. Background

1. The Poison Prevention Packaging Act of 1970 and CPSC's Implementing Regulations

The Poison Prevention Packaging Act of 1970 (PPPA), 15 U.S.C. 1471–1476, gives the Commission authority to establish standards for the ''special packaging'' of household substances, such as drugs, when child-resistant (CR) packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance, and the special packaging is technically feasible, practicable, and appropriate for such substance. 15 U.S.C. 1472(a). Special packaging requirements under the PPPA have been codified at 16 CFR parts 1700 and 1702. Specifically, CPSC regulations require special packaging for oral prescription drugs. 16 CFR 1700.14(a)(10). CPSC regulations allow companies to petition the Commission for an exemption from CR requirements. 16 CFR part 1702.

Two of the three ''reasonable grounds'' [1] for granting an exemption from the special packaging requirements are: (1) that the degree or nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance; or (2) special packing is not technically feasible, practicable, or appropriate for the subject substance. 16 CFR 1702.17(a) and (b).

If the Commission determines that a petition presents reasonable grounds for an exemption, CPSC regulations require publication in the **Federal Register** of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue would be exempt. 16 CFR 1702.17.

2. The Product for Which an Exemption Is Sought

On March 30, 2020, Genentech, Inc. (Genentech), petitioned the Commission to exempt two specified sized tablets of baloxavir marboxil, which it markets as XOFLUZA, from the special packaging requirements for oral prescription drugs. The U.S. Food and Drug Administration (FDA) approved XOFLUZA in October 2018, with a two-tablet dose for acute uncomplicated flu in patients older than 12 years old showing symptoms for less than 48 hours. FDA approved single tablet doses in March 2021. XOFLUZA has been marketed in tablet form and is currently dispensed in CR packaging. The petitioner asserted that an exemption from special packaging is justified because of the lack of toxicity and lack of adverse human experience with the drug. The petitioner also claimed that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA.

Genentech represents that it intends to continue U.S. production and packaging of XOFLUZA if the petition is granted. The firm also states that grant of the petition would allow it to use a packaging site in Kaiseraugst, Switzerland, as a back-up facility for the U.S. market in the event there is a spike in demand for XOFLUZA over a short period of time.

In September 2021, after considering the information provided by the petitioner up to that date and other available toxicity and human experience data, the Commission preliminarily concluded in the preamble of the Notice of Proposed Rulemaking (NPR) that the ''lack of toxicity and lack of adverse human experience for the substance'' presented by the availability of 40 mg and 80 mg tablets of baloxavir marboxil (currently marketed as XOFLUZA) is such that special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 86 FR 51640, at 54641–42 (September 16, 2021); 16 CFR 1702.17(a). However, the Commission preliminarily found that the petitioner's request for an exemption from special packaging, on the basis that it is not technically feasible, practicable, or appropriate for XOFLUZA, was not warranted based on the information provided by the petitioner. Based on the lack of toxicity, the Commission determined that reasonable grounds for an exemption were presented and voted to grant the petition and begin a rulemaking proceeding to exempt baloxavir marboxil tablets in packages containing not more than 80 mg of the drug from the special packaging requirements for oral prescription drugs.

B. Toxicity and Injury Data for XOFLUZA

1. Summary of Data From Proposed Rule

Toxicity

Staff reviewed the toxicity of XOFLUZA. XOFLUZA has been studied in pediatric patients.[2] Overall, clinically relevant doses of XOFLUZA (40 or 80 mg total dose) in humans are well tolerated.[3]

[1] The third reasonable ground for an exemption is that special packaging is incompatible with the particular substance. 16 CFR 1702.17(c). The petitioner has not requested an exemption on this basis, so it is not relevant here.

[2] Hirotsu N. (2019). Baloxavir Marboxil in Japanese Pediatric Patients with Influenza: Safety and Clinical and Virologic Outcomes. Clin Infect Dis Aug 14;71(4):971–981.; Heo Y–A. (2018). Baloxavir: First Global Approval. Drugs 78:693 697.;*https://clinicaltrials.gov/ct2/show/NCT03653364;* XOFLUZA Prescribing Information, 2021; Hayden F.G. (2018). Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. The New England Journal of Medicine.379:(10); Dziewiatkowski N.A., Osmon E.N., Chahine E.B., Thornby K.A. (2019). Baloxavir: a novel single-dose oral antiviral for the treatment of influenza. Sr Care. Pharm; 34:243–52.

[3] Dziewiatkowski N.A., Osmon E.N., Chahine E.B., Thornby K.A. (2019). Baloxavir: a novel single-dose oral antiviral for the treatment of influenza. Sr Care. Pharm; 34:243–52.; Taieb V., Ikeoka, Fang-Fang Ma H., Borkowski K., Aballea S., Tone Keiko and Hirotsu N. (2019). A network meta-analysis of the efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors for the treatment of influenza in otherwise healthy patients; Current Medical Research and Opinion 35:8, 1355–1364.;

The analysis of total adverse events (AE) included 10 studies [4] with six treatments and 5,628 patients. AE did not differ significantly between placebo and XOFLUZA. For drug-related vomiting, 3,297 patients from five studies were included. XOFLUZA did not differ from placebo in these studies. The percentage of patients experiencing any AE of 610 patients (12 to 64 years old) in the CAPSTONE 1 clinical trial was 1.0% grade 3 or grade 4, which can be categorized as not serious. The adverse events experienced were diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in the level of aspartate aminotransferase (AST, headache, vomiting, dizziness, leukopenia, and constipation. Five deaths have been reported by the Adverse Event Reporting System (AERS); [5] however, staff assessed that these deaths were not caused by XOFLUZA.

The most common AE of the correct dose of XOFLUZA is diarrhea.[6] The XOFLUZA Product Information, 2021 reported that diarrhea (3%), bronchitis (3%), nausea (2%), headache (1%) were the most significant adverse events found. Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring of vital signs and observations of the clinical status of the patient.[7] There is no specific antidote for overdose with XOFLUZA, and it is unlikely to be significantly removed by dialysis because it is highly protein bound.[8] Two overdoses of XOFLUZA were reported in children under 5 years old in the FAERS data. Neither overdose resulted in serious injury or death; one of the children experienced malaise and the other child experienced a rash.

Overall, treatment with XOFLUZA is well tolerated. In drug trials, XOFLUZA was well-tolerated as a treatment for flu in otherwise healthy children age 1 to less than 12 years old. Additionally, two Phase 3 pediatric studies in Japan demonstrate that XOFLUZA is well tolerated across all pediatric age groups. Finally, the FDA concluded there are no safety concerns for children from Phase I, Phase 2, and Phase 3 trials of XOFLUZA. If accidentally ingested, the most likely symptoms are diarrhea, nausea, or headache. For these reasons, staff determined that XOFLUZA will not cause serious injury or death upon acute exposure by a child under 5 years old.

Injury Data

The NPR explained that CPSC staff had searched the Consumer Product Safety Risk Management System (CPSRMS) and the National Electronic Injury Surveillance System (NEISS) databases, and reviewed reports from FDA related to adverse events associated with XOFLUZA. Staff found no incidents related to XOFLUZA in CPSRMS or NEISS from January 2015 through December 2020.

2. Updated Injury Data Since NPR

Since publication of the NPR staff has done an updated search and found no incidents related to XOFLUZA in the CPSRMS and NEISS databases from January 2021 through March 2024. CPSC staff also reviewed 26 reports received from FDA related to AEs associated with XOFLUZA between January of 2018 through March 2024. Of these 26 reports, there were 8 nonserious reports, such as off-label use of XOFLUZA. There were also 18 reported AEs. All of these AEs, such as febrile seizures, delirious behaviors, and gastrointestinal bleeding, were assessed by staff to be due to the flu disease progression and not due to XOFLUZA. The staff briefing package on this final rule provides more detailed information.[9]

C. Response to Comments on the Proposed Rule

Two comments were submitted in response to the publication of the NPR. One comment stated that XOFLUZA should not be exempt from child-resistant packaging because there is little-to-no existing human toxicity data for age groups 0–12 years old, and asserted there is a risk of allergic reactions (including anaphylaxis, angioedema, urticaria, and erythema multiforme). In response to this comment, CPSC staff advises that a drug trial demonstrated that XOFLUZA is a well-tolerated potential treatment for the flu in otherwise healthy children within the age range of 1 year and over to 12 years and under. Additionally, two Phase 3 pediatric studies conducted in Japan demonstrate that XOFLUZA is well tolerated across all pediatric age groups. Finally, the FDA concluded there are no safety findings of concern for children from Phase 1, Phase 2, or Phase 3 trials of XOFLUZA. Indeed, as compared to adults, drugs are less common triggers of anaphylaxis in children, with a frequency which is increasing from infancy to adolescence.[10] Of the 26 adverse reactions in the FDA FAERS data, there were no hypersensitivity reactions in children under 5 years of age.[11]

The second comment stated that people should use zinc instead of XOFLUZA for treatment of the flu. The use of other substances to treat the flu is not relevant to whether baloxavir marboxil should be given an exemption from the special packing requirements and, therefore, is outside the scope of this rulemaking.

D. Description of the Final Rule

The final rule amends 16 CFR part 1700 to include a new exemption from the special packaging requirements for baloxavir marboxil tablets in packages

Hayden F.G. (2018).; Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. The New England Journal of Medicine.379:(10).

[4] Taieb V., Ikeoka, Fang-Fang Ma H., Borkowski K., Aballea S., Tone Keiko and Hirotsu N. (2019). A network meta-analysis of the efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors for the treatment of influenza in otherwise healthy patients. Current Medical Research and Opinion 35:8, 1355–1364.

[5] AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

[6] Heo Y–A. (2018). Baloxavir: First Global Approval. Drugs 78:693–697.; Shionogi & Co. Ltd. Xofluza (baloxavir marboxil) tablets 10 mg/20mg approved for the treatment of influenza types A and B in Japanese [media release] 23 Feb 2018.

[7] (PoisIndex, 2021).

[8] Prescribing Information for XOFLUZA, 2021; Micromedex Solutions, Poisindex Xofluza search 2/1/2021.

[9] The staff briefing package is available here: *https://www.cpsc.gov/s3fs-public/Briefing-Package-Final-Rule-to-Exempt-Xofluza-from-Special-Packaging-Requirements-in-the-PPPA.pdf?VersionId=rr6qgyEz7Tjc_1AHXq6OndQHRzIaCFgX.*

[10] Cardinale F, Amato D, Mastrototaro MF, Caffarelli C., Crisafulli D., Franceshini F., Liotti L., Bottau P., Saretta F., Mori F. and Bernardini R. Drug-induced anaphylaxis in children. Acta Biomed. 2019 90 (3–S): 30–35.; Atanaskovic-Markovic M, Gomes E, Cernadas JR, du Toit G, Kidon M, Kuyucu S, Mori F, Ponvert C, Terreehorst I, Caubet JC. Diagnosis and management of drug-induced anaphylaxis in children: An EAACI position paper. Pediatric Allergy Immunol. 2019 May;30(3):269–276.). In the pediatric population the average age of diagnosis for drug-induced hypersensitivity was 8.7 years old. The most common causative drugs included antiepileptics (50%) and antibiotics (30.8%) (Metterle L, Hatch L, Seminario-Vidal L. Pediatric drug reaction with eosinophilia and systemic symptoms: A systemic review of the literature, with a focus on relapsing cases. Pediatric Dermatol. 2020 Jan;37(1):124–129. doi: 10.1111/pde.14044. Epub 2019 Nov 5., Oberlin KE, Rahnama-Moghadam S, Alomari AK, Haggstrom AN. Drug reaction with eosinophilia and systemic symptoms: Pediatric case series and literature review. Pediatric Dermatol. 2019 Nov;36(6):887–892.). Pediatric drug reaction with eosinophiliea and systemic symptoms is an uncommon disease with a mean age of 11.5 years of age presenting with the syndrome (Oberlin KE, Rahnama-Moghadam S, Alomari AK, Haggstrom AN. Drug reaction with eosinophilia and systemic symptoms: Pediatric case series and literature review. Pediatric Dermatol. 2019 Nov;36(6):887–892.).

[11] *https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.*

containing not more than 80 mg of the drug in proposed 1700.14(a)(10)(xxiv).[12] The exemption is intended to cover baloxavir marboxil tablets in a dosage of 80 mg or less. The text of the final rule is unchanged from the proposed rule. The final rule makes no other changes to part 1700.

E. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (RFA; 5 U.S.C. 601 *et seq.*), an agency that engages in rulemaking generally must prepare initial and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605(b) of the Act provides that an agency is not required to prepare an RFA if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

As noted in the preamble to the proposed rule (86 FR 51640 at 51642), the Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of the proposed rule. Based on this assessment, the Commission preliminarily concluded that the proposed rule would not have a significant impact on a substantial number of small businesses or other small entities. We received no comments on this assessment or any additional information. Therefore, we certify that the rule will not have a significant economic impact on a substantial number of small entities. 5 U.S.C. 605(b).

F. Effective Date

The Administrative Procedure Act (APA) generally requires that a substantive rule must be published not less than 30 days before its effective date. 5 U.S.C. 553(d)(1). The NPR proposed an effective date of 30 days after publication of the final rule in the **Federal Register**. We received no comments on the proposed effective date. Therefore, the effective date for the final rule will be May 20, 2024.

G. Environmental Considerations

The Commission's regulations provide a categorical exclusion from any requirement to prepare an environmental assessment or an environmental impact statement the Commission rules ''have little or no potential for affecting the human environment.'' 16 CFR 1021.5(c)(3). Rules exempting products from poison prevention packaging rules fall within the categorical exclusion, so no environmental assessment or environmental impact statement is required.

H. Preemption

The PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, ''no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard.'' 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if (1) the state or local standard provides a significantly higher degree of protection from the risk of injury or illness than the PPPA standard and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA's preemption clause and the Commission grants the exemption through a process specified at 16 CFR part 1061. 15 U.S.C. 1476(c)(1). In addition, the Federal government, or a State or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for that government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the final rule exempting baloxavir marboxil tablets in packages containing not more than 80 mg of the drug from special packaging requirements preempts nonidentical state or local special packaging standards for the substance.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, the Commission amends 16 CFR part 1700 as follows:

PART 1700—[AMENDED]

■ 1. The authority citation for part 1700 continues to read as follows:

Authority: 15 U.S.C. 1471–76. Secs. 1700.1 and 1700.14 also issued under 15 U.S.C. 2079(a).

■ 2. Section 1700.14 is amended by adding paragraph (a)(10)(xxiv) to read as follows:

§ 1700.14 Substances requiring special packaging.

(a) * * *

(10) * * *

(xxiv) Baloxavir marboxil tablets in packages containing not more than 80 mg of the drug.

* * * * *

Alberta E. Mills,

Secretary, U.S. Consumer Product Safety Commission.

[FR Doc. 2024–07651 Filed 4–18–24; 8:45 am]

BILLING CODE 6355–01–P

[12] The Commission voted 4–1 to publish this final rule. The Record of Commission Action can be viewed here: *https://www.cpsc.gov/s3fs-public/RCA-Draft-Final-Rule-to-Exempt-Baloxavir-Marboxil-XOFLUZA-from-Packaging-Requirements-in-PPPA.pdf?VersionId=TR31D0KETbniRXpLZHUqI_9R28VqffJo.*

SECURITIES AND EXCHANGE COMMISSION

17 CFR Part 232

[Release Nos. 33–11277; 34–99752; 39–2554; IC–35155]

Adoption of Updated EDGAR Filer Manual

AGENCY: Securities and Exchange Commission.

ACTION: Final rule.

SUMMARY: The Securities and Exchange Commission (''Commission'') is adopting amendments to Volume II of the Electronic Data Gathering, Analysis, and Retrieval system Filer Manual (''EDGAR Filer Manual'' or ''Filer Manual'') and related rules and forms. EDGAR Release 24.1 will be deployed in the EDGAR system on March 18, 2024.

DATES: *Effective date:* April 19, 2024. The incorporation by reference of the revised Filer Manual is approved by the Director of the **Federal Register** as of April 19, 2024.

FOR FURTHER INFORMATION CONTACT: For questions regarding the amendments to Volume II of the Filer Manual, please contact Rosemary Filou, Deputy Director and Chief Counsel, Laurita Finch, Senior Special Counsel, or Lidian Pereira, Senior Special Counsel, in the EDGAR Business Office at (202) 551–3900. For questions regarding the Inline eXtensible Business Reporting Language (''Inline XBRL'') mandate for filing financial statements and schedules required by Form 11–K, please contact the Office of Rulemaking in the Division of Corporation Finance at (202) 551–3430. For technical questions concerning Inline XBRL, please contact the Office of Structured Disclosure in the Division of Economic and Risk Analysis at (202) 551–5494. For questions regarding the filing of submission form types 17AD–27 and 17AD–27/A in an Inline XBRL format that includes the data elements described in Rule 17Ad-27(b)(1) through