United States
Consumer Product Safety Commission

THIS DOCUMENT HAS BEEN ELECTRONICALLY APPROVED AND SIGNED.

Ballot Vote Sheet

TO: The Commission
Alberta E. Mills, Secretary

DATE: March 27, 2024

THROUGH: Jessica L. Rich, General Counsel
Austin C. Schlick, Executive Director

FROM Daniel R. Vice, Assistant General Counsel, Regulatory Affairs
David M. DiMatteo, Attorney, Regulatory Affairs

SUBJECT: Draft Final Rule to Exempt Baloxavir Marboxil (XOFLUZA™) in Packages Containing Not More than 80 mg of the Drug from Special Packaging Requirements of the Poison Prevention Packaging Act

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BALLOT VOTE DUE: Tuesday, April 2, 2024

The Office of the General Counsel (OGC) is forwarding a draft final rule exempting baloxavir marboxil in packages containing not more than 80 mg of the drug from special packaging requirements under the Poison Prevention Packaging Act (PPPA). The rulemaking is based on a petition submitted by Genentech, Inc. to exempt two specified sized tablets of baloxavir marboxil, which it markets as XOFLUZA, from the special packaging requirements for oral prescription drugs. The Commission previously voted to grant the petition and publish a notice of proposed rulemaking. Attached for Commission consideration is a draft final rule *Federal Register* notice. If approved by the Commission, OGC will send the notice to the *Federal Register* for publication.

Please indicate your vote on the following options:

I. Approve publication of the attached notice in the *Federal Register*, as drafted.

_____ _____
(Signature) (Date)

U.S. Consumer Product Safety Commission
4330 East-West Highway
Bethesda, MD 20814

National Product Testing and Evaluation Center
5 Research Place
Rockville, MD 20850

II. Approve publication of the attached notice in the *Federal Register*, with the specified changes.

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_____ _____

(Signature) (Date)

III. Do not approve publication of the attached notice in the *Federal Register*.

_____ _____

(Signature) (Date)

IV. Take other action specified below.

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_____

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_____ _____

(Signature) (Date)

Attachment: Draft Final Rule: “Poison Prevention Packaging Requirements; Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More than 80 mg of the Drug”

[Billing Code 6355-01-P]

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 [**insert date 30 days after publication in the FEDERAL REGISTER**].

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

[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.

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 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 (Sept. 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 upon 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]

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-

[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.; 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.

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 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

[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.

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]

[9] The staff briefing package is available here: [INSERT HYPERLINK HERE].

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

[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] FDA Adverse Event Reporting System (FAERS) Public Dashboard | FDA.

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 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 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).

[12] The Commission voted X–X to publish this notification.

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 [**insert date 30 days after publication in the FEDERAL REGISTER**].

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:

Sec. 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

Briefing Package

Final Rule to Exempt Baloxavir Marboxil (XOFLUZA™) (PP 20-1) from the Special Packaging Requirements of the Poison Prevention Packaging Act

For Information:
Cheryl Scorpio, Ph.D.
Directorate for Health Sciences

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Executive Summary

"Special" or child-resistant packaging (CR packaging or CRP) is required for oral prescription drugs under the Poison Prevention Packaging Act (PPPA) and its implementing regulation (16 C.F.R. § 1700.14(a)(10)). The Commission's regulations allow exemptions from this requirement for substances with low acute toxicity (16 C.F.R. part 1702).

In March 2020, Genentech, Inc. submitted a petition to the Commission seeking to exempt baloxavir marboxil (XOFLUZA™) tablets, at a dose of not more than 80 mg, from the special packaging requirements of the PPPA. XOFLUZA is an antiviral medication used to treat influenza.

In September 2021, the Commission voted to grant the petition and publish a notice of proposed rulemaking (NPR), proposing to codify the special packaging exemption in the Commission's PPPA regulations. The NPR was published in the Federal Register on September 16, 2021. Two comments were submitted in response to the NPR. One comment opposed the proposed rule and the other presented arguments outside the scope of the rulemaking. Since publication of the NPR, staff has received no information that changes its recommendation to grant the petition.

Staff determined that available data support that XOFLUZA has low oral toxicity. Moreover, there have been no serious adverse event data associated with accidental ingestion. The acute toxicity of XOFLUZA is mild and may include diarrhea, nausea, and headache. Thus, staff concludes that the petitioner has shown that "special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance." Therefore, staff concludes that the firm has met the requirements to receive an exemption from the special packaging requirements under 16 C.F.R. § 1702.17(a).

Staff recommends that the Commission issue a final rule to exempt from the CRP requirements baloxavir marboxil (XOFLUZA) tablets containing not more than 80 mg of the drug.

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Briefing Memorandum March 27, 2024

To: The Commission
Alberta E. Mills, Secretary

Through: Jessica Rich, General Counsel
Austin C. Schlick, Executive Director

From: Duane Boniface, Assistant Executive Director
Office of Hazard Identification and Reduction

Cheryl Scorpio, Ph.D., Project Manager
Directorate for Health Sciences

Subject: Final Rule to Exempt Baloxavir Marboxil Tablets Containing Not More than 80 mg of the Drug from the Special Packaging Requirements of the Poison Prevention Packaging Act (PPPA)

I. Introduction

The PPPA requires "special packaging" or CRP for certain "household substances," with requirements codified at 16 C.F.R. § 1700 and 16 C.F.R. part 1702. Specifically, the PPPA requires that the Commission issue regulations mandating special packaging of a household substance if:

> (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance; and
> (2) the special packaging to be required by such standard is technically feasible, practicable, and appropriate for such substance.

15 U.S.C. § 1472(a).

CPSC has implemented this provision of the PPPA by promulgating a regulation requiring special packaging for oral prescription drugs, among other substances. 16 C.F.R. § 1700.14(a)(10). The Commission's regulations allow a firm to petition for an exemption from the special packaging requirements for several reasons, including that a substance has a "lack of toxicity and lack of

adverse human experience for the substance [that] clearly supports granting the exemption," 16 C.F.R. § 1702.7(a), or that "special packaging is not technologically feasible, practicable, or appropriate for the substance." 16 C.F.R. § 1702.7(b). Either one of these reasons may be a basis for granting an exemption. If the Commission determines that reasonable grounds for an exemption are presented by the petition, 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 is exempt. 16 C.F.R. § 1702.17.

In March 2020, Genentech, Inc. submitted a petition requesting to exempt the tablet forms of their drug, XOFLUZA™ (baloxavir marboxil) from CRP requirements. The Federal Drug Administration (FDA) approved XOFLUZA in October 2018, with a two-tablet dose for the acute uncomplicated flu in patients older than 12 years old showing symptoms for less than 48 hours. In March 2021, the FDA approved single-tablet doses of XOFLUZA. Currently, XOFLUZA is in tablet form and dispensed in CRP.

The petitioner asserts that there are reasonable grounds for an exemption from PPPA special packaging requirements because: (1) special packaging is not required to protect children from serious illness resulting from ingesting XOFLUZA; and (2) special packaging is not technically feasible, practicable, or appropriate for XOFLUZA.

The petitioner intends to continue U.S. production and packaging of XOFLUZA and reports they have had conversations with the Administration for Strategic Preparedness and Response regarding the Strategic National Stockpile, and they intend to add a back-up packaging site in Kaiseraugst, Switzerland, for the U.S. market. This facility would be used, for example, in the event that there is a spike in demand for XOFLUZA over a short period of time (https://www.regulations.gov/document/CPSC-2021-0027-0003)

Staff under the direction of Project Manager Cheryl Scorpio have concluded that CRP is not necessary for XOFLUZA tablets in packages containing not more than 80 mg of the drug because of low acute toxicity and the lack of serious adverse human experience data associated with acute ingestion. Therefore, because of the lack of toxicity and lack of adverse human experience for the substance, staff recommended in the NPR that special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 C.F.R. § 1702.17(a).

Staff concluded, though, that the petitioner has *not* demonstrated that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA, and therefore, granting the petition request for an exemption on that basis is not justified under 16 C.F.R. § 1702.17(b).

Based on the staff's analysis, the Commission granted the petition and published an NPR in the Federal Register (86 Fed. Reg. 51,640) on September 16, 2021, to exempt from the CRP

requirement of the PPPA baloxavir marboxil in packages containing not more than 80 mg of the drug.[1]

II. Discussion

A. Public Comments

There were two comments submitted in response to the NPR. One comment asserted that XOFLUZA should not be exempt from child-resistant packaging because there are little-to-no existing human toxicity data for age groups 0-12 years old and claimed that there is a risk of allergic reactions (including anaphylaxis, angioedema, urticaria, and erythema multiforme).

The second comment was outside the scope of the rulemaking. The comment recommended using zinc instead of XOFLUZA™ for the flu. The use of other substances to treat the flu is not relevant to whether baloxavir marboxil (XOFLUZA) should be given an exemption from the special packing requirements and therefore was not considered to be within the scope of this rulemaking.

CPSC staff's response (Tab A) notes that a drug trial demonstrated that XOFLUZA was a well-tolerated potential treatment for the flu in otherwise healthy children age 1 to less than 12 years old. Additionally, two Phase 3[2] 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.

B. Injury Data

In the staff briefing package for the NPR, the Division of Epidemiology reported on a search of the CPSRMS and NEISS databases, and reviewed FDA reports related to adverse events associated with XOFLUZA. CPSC staff found no incidents related to XOFLUZA in CPSRMS[3] or NEISS[4]

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[1] https://www.federalregister.gov/documents/2021/09/16/2021-19953/poison-prevention-packaging-requirements-proposed-exemption-of-baloxavir-marboxil-tablets-in.

[2] A Phase 1 clinical trial is the first time a drug is tested in humans. Its purpose is to reproduce the preclinical trial data in humans. A Phase 2 clinical trial determines the right drug dosage and establishes the drug safety in participants with the symptoms the drug is proposed to treat. A Phase 3 clinical trial occurs in many segments (*e.g.*, men, women, and children) of a large population. Its purpose is to confirm the safety and efficacy of the study drug and determine its side effects.

[3] Staff searched the CPSC databases of CPSRMS. These reported deaths and incidents are not intended to be a complete count of all that occurred during this period. However, they do provide a basis for a minimum number of deaths and incidents occurring during this period. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

[4] NEISS injury data are gathered from emergency departments of hospitals selected as a probability sample of all U.S. hospitals with emergency departments. The surveillance data gathered from the sample hospitals enable the CPSC staff to make timely national estimates of the number of injuries associated with specific consumer products. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

from January 2015 through December 2020. No incidents related to XOFLUZA were found during this time frame.

After the publication of the NPR, CPSC staff reviewed 26 reports received from FDA related to adverse events (AEs) associated with XOFLUZA. 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, involving effects such as febrile seizures, delirious behaviors and gastrointestinal bleeding, were assessed by staff to be due to the flu disease progression and not to XOFLUZA.

Staff also did a search after the publication of the NPR and found no incidents related to XOFLUZA in the CPSRMS and NEISS databases from January 2021 through March 2024.

C. Economic Information

The Directorate for Economic Analysis provided the updated memorandum in Tab B.
Staff finds that the proposed exemption for baloxavir marboxil will not have a significant economic impact on a substantial number of small entities.

D. Effective Date

The NPR proposed a relatively early effective date of 30 days after the date of publication of the final rule in the Federal Register because the proposed rule would provide an exemption from the requirement to use special packaging for baloxavir marboxil tablets in packages containing not more than 80 mg of the drug and does not impose any new requirement. No comments were submitted regarding the proposed effective date. Therefore, if the Commission issues a final rule to exempt baloxavir marboxil from the requirements of the PPPA, staff recommends that the final rule take effect 30 days after publication in the Federal Register.

III. Options

1. The Commission may issue a final rule exempting from the special packaging requirements baloxavir marboxil tablets in packages containing not more than 80 mg of the drug, if it concludes that that petition presents reasonable grounds for an exemption, namely, that baloxavir marboxil will not present a risk of serious personal injury or serious illness to young children when packaged in non-CR packaging.

2. The Commission may decline to issue a final rule exempting from the special packaging requirements baloxavir marboxil tablets in packages containing not more than 80 mg of the drug if it concludes that the petition does not present reasonable grounds for an exemption.

If the Commission does not take either of these actions, then Genentech's petition for relief from the special packaging requirements will remain pending before CPSC.

IV. Staff's Conclusions and Recommendation

Staff concludes that special packaging is not necessary for baloxavir marboxil tablets in packages containing not more than 80 mg of the drug because of low acute toxicity and the lack of serious adverse human experience data associated with acute ingestion. Therefore, because of the lack of toxicity and lack of adverse human experience for the substance, special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 C.F.R. § 1702.17(a). Based on the above analysis, staff recommends that the Commission issue a final rule to exempt from CRP baloxavir marboxil tablets in packages containing not more than 80 mg of the drug.

TAB A: Public Comments to the NPR

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Date: March 27, 2024

To: Cheryl Scorpio, Ph.D.,
Pharmacologist, Project Manager
Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

Through: Mary Kelleher,
Associate Executive Director
Directorate for Health Sciences

Stefanie Marques, Ph.D.,
Director, Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

From: Adrienne Layton, Ph.D.,
Pharmacologist, Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

Subject: Response to Public Comments on the NPR

Two comments were submitted in response to the NPR.

The first comment (CPSC-2021-0027-0002) asserted that XOFLUZA should not be exempt from the child-resistant packaging requirement because there is little-to-no existing human toxicity data for age groups 0-12 years old and claimed that there is a risk of allergic reactions (including anaphylaxis, angioedema, urticaria, and erythema multiforme).

The second comment (CDC-2020-0081-4265) recommended using zinc instead of XOFLUZA™ for the flu. This comment is outside the scope of the NPR. The use of other substances like zinc to treat the flu is not relevant to whether baloxavir marboxil (XOFLUZA) should be given an exemption from the special packing requirements.

Comment response:

Staff disagrees with the first comment because there have been studies assessing the safe use of XOFLUZA in children. The primary objective of the miniSTONE-2 trial was to demonstrate the safety of XOFLUZA. The trial demonstrated that XOFLUZA was comparable to oseltamivir

(Tamiflu) in time to alleviate influenza signs and symptoms. The study also showed that XOFLUZA was a well-tolerated potential treatment for the flu in otherwise healthy children age 1 to less than 12 years old. The proportion of adverse events (AEs) related to the study drug were similar between the XOFLUZA and oseltamivir placebo groups. No serious adverse events (SAEs) or deaths occurred in the study, and the most common AEs, occurring in both groups were gastrointestinal related (*i.e.*, diarrhea or vomiting (Baker, 2020)). Additionally, two Phase 3 pediatric studies conducted in Japan demonstrate that XOFLUZA is well tolerated across all pediatric age groups.

More broadly, staff is not aware of any incidents involving death or serious injury as a result of accidental ingestion of XOFLUZA by adults or children.

As compared to adults, drugs are less common triggers of anaphylaxis in children, with a frequency which is increasing from infancy to adolescence (Cardianale,2019; Atanaskovic, 2019). In the pediatric population the average age of diagnosis for drug-induced hypersensitivity was 8.7 years old. The most common causative drugs include antiepileptics (50%) and antibiotics (30.8 %) (Metterle, 2020, Oberlin, 2019). Pediatric drug reaction with eosinophilia and systemic symptoms is an uncommon disease with a mean age of 11.5 years of age presenting with the syndrome (Oberlin, 2019). Of 26 adverse reactions in the FDA FAERS data there were no hypersensitivity reactions in children under 5 years of age (FDA Adverse Event Reporting System (FAERS) Public Dashboard | FDA).

Finally, the FDA concluded there are no safety findings of concern for children from Phase 1, Phase 2, or Phase 3 trials of XOFLUZA. A total of 117 children (8% of all subjects) were enrolled in Trial 1601T0831 and randomized to either XOFLUZA (N=76) or placebo (N=41) treatment groups. Three percent or less of the children exhibited diarrhea, bronchitis, nasopharyngitis, nausea, headache or sinusitis, (FDA Clinical Report of XOFLUZA Application 210854 Orig1S000), which are not serious personal injuries or illnesses (PPPA**,** 15 U.S.C. 1471-1476).

References:

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Baker J, Block SL et al., Baloxavir Marboxil: Single-Dose Treatment in Influenza-Infected Children: A Randomized, Double-Blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2) Pediatric Infect Dis J. 2020 Aug;39(8):700-705.

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.

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Oberlin KE, Rahnama-Moghadam S, Alomari AK, Haggstrom AN. Drug reaction with eosinophilia and systemic symptoms: Pediatric case series and literature review. Pediatr Dermatol. 2019 Nov;36(6):887-892.

Rahnama-Moghadam S, Alomari AK, Haggstrom AN. Drug reaction with eosinophilia and systemic symptoms: Pediatric case series and literature review. Oberlin KE, Pediatr Dermatol. 2019 Nov;36(6):887-892. doi: 10.1111/pde.13949. Epub 2019 Aug 18.

TAB B: Final Rule for the Exemption of Baloxavir Marboxil (XOFLUZA™) from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act– Small Business Considerations

THIS DOCUMENT HAS NOT BEEN
REVIEWED OR ACCEPTED BY THE COMMISSION

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Date: March 27, 2024

To: Cheryl Scorpio, Ph.D.
Pharmacologist, Project Manager
Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

Through: Alex Moscoso
Associate Executive Director
Directorate for Economics

From: Cynthia Gillham
Economist
Directorate for Economics

Subject: Final Rule for the Exemption of Baloxavir Marboxil (XOFLUZA™) from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Small Business Considerations

Introduction

On September 16, 2021, the Commission published a notice of proposed rulemaking (NPR) "Proposed Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More Than 80 mg of the Drug" published in the Federal Register (86 Fed. Reg. 51,640).[5] No comments were submitted to the NPR regarding the economic impact of the proposed CR exemption.

Small Business Considerations

Staff concluded in the NPR that the Child-Resistant (CR) packaging exemption for baloxavir marboxil (XOFLUZA) is unlikely to impact a substantial number of small firms.[6] However, staff requested public comment on any small business impacts that might result that had not been considered.

[5] https://www.federalregister.gov/documents/2021/09/16/2021-19953/poison-prevention-packaging-requirements-proposed-exemption-of-baloxavir-marboxil-tablets-in

[6] Staff Briefing Package, Petition to Exempt XOFLUZA™ (PP 20-1) from the Special Packaging Requirements of the Poison Prevention Packaging Act, TAB D, September 2, 2021, pp. 51-56.

During the public comment period for the NPR, no comments were submitted regarding small business impacts that might result from exempting baloxavir marboxil (XOFLUZA) from CR-packaging requirements. Therefore, for the reasons stated in the NPR, and with no public comment to the contrary, staff finds that the exemption will not have a significant economic impact on a substantial number of small entities.

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REVIEWED OR ACCEPTED BY THE COMMISSION