NEW DRUG APPROVAL

Brand Name	Tembexa®
Generic Name	brincidofovir
Drug Manufacturer	Chimerix, Inc.

New Drug Approval

FDA approval date: August 3, 2021

Review designation: Priority; Orphan

Type of review: Type 2 - New Active Ingredient; New Drug Application (NDA): 214460

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Smallpox is a serious, contagious, and sometimes deadly disease caused by the variola virus. Smallpox outbreaks occurred for thousands of years, but the disease was eliminated from the world after a successful vaccination campaign. People with smallpox had a fever and a distinctive skin rash. Although most people with smallpox recovered, about three out of every ten people with the disease died.

Thousands of years ago, variola virus (smallpox virus) emerged and began causing illness and deaths in human populations, with smallpox outbreaks occurring from time to time.

The origin of smallpox is unknown. The finding of smallpox-like rashes on Egyptian mummies suggests that smallpox has existed for at least 3,000 years. The earliest written description of a disease like smallpox appeared in China in the 4th century CE (Common Era). Early written descriptions also appeared in India in the 7th century and in Asia Minor in the 10th century.

The last natural outbreak of smallpox in the United States happened in 1949. The last naturally spread case in the entire world happened in 1977. The World Health Assembly declared smallpox eradicated in 1980. Even a single confirmed case of smallpox today would be considered an emergency.

Efficacy

The effectiveness of Tembexa® for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible and inducing smallpox disease in humans to study the efficacy of the drug is not ethical. Therefore, the effectiveness of Tembexa® for treatment of smallpox disease was established based on results of adequate and well-controlled animal efficacy studies of rabbits and mice infected with species specific non-variola orthopoxviruses. Survival rates observed in the animal studies may not be predictive of survival rates in clinical practice.

Study Design: Efficacy studies were conducted in the rabbitpox model (New Zealand White rabbits infected with rabbitpox virus) and the mousepox model (BALB/c mice infected with ectromelia virus).

The primary efficacy endpoint for these studies was survival. Survival was monitored for 4 to 5 times the mean time to death for untreated animals in each model.

In the rabbitpox study, rabbits were lethally challenged intradermally with 600 plaque-forming units of rabbitpox virus; brincidofovir was administered orally with a regimen of 20/5/5 mg/kg (administered every 48 hours for 3 doses) with brincidofovir treatment initiated on 3-, 4-, 5-, or 6-days post-challenge. The timing of brincidofovir

dosing was intended to assess efficacy when treatment is initiated after animals have developed clinical signs of disease, specifically fever in rabbits. Clinical signs of disease were evident in some animals at Day 3 post-challenge but were evident in all animals by Day 4 post-challenge.

In the mousepox study, mice were lethally challenged intranasally with 200 plaque-forming units of ectromelia virus; brincidofovir was administered orally with a regimen of 20/5/5 mg/kg or 10/5/5 mg/kg (administered every 48 hours for 3 doses) with brincidofovir treatment initiated on 4-, 5-, 6-, or 7-days post-challenge. All animals had detectable viremia by 4 days post-challenge. In the mousepox model, a clinically evident sign of disease could not be identified to use as a trigger to initiate treatment.

Study Results: Treatment with brincidofovir resulted in statistically significant improvement in survival relative to placebo, except when the 10/5/5 mg/kg regimen was initiated at Day 6 post-challenge in the mousepox study (Table 1).

Table 1: Survival Rates in Brincidofovir Treatment Studies in the Rabbitpox and Mousepox Models

Dose Regimen (mg/kg)	Treatment Initiation Day	Survival % (# survived/n)		Survival Rate Difference (95% CI)[a]	p-value[b]
		Placebo	Brincidofovir		
Rabbitpox[c]					
Study 1	Day 4	29% (8/28)	90% (26/29)	61% (36%, 79%)	<0.0001
	Day 5		69% (20/29)	40% (12%, 63%)	0.0014
	Day 6		69% (20/29)	40% (12%, 63%)	0.0014
Mousepox[d]					
Study 2	Day 4	13% (4/32)	78% (25/32)	66% (44%, 82%)	<0.0001
	Day 5		66% (21/32)	53% (29%, 72%)	<0.0001
	Day 6		34% (11/32)	22% (1%, 43%)	0.0233[e]

a. Survival percentage with brincidofovir-treated animals minus survival percentage in placebo-treated animals. Exact confidence intervals are presented.
b. P-value is from 1-sided Boschloo test compared with placebo.
c. 20/5/5 mg/kg (fully effective dose in the rabbitpox model)
d. 10/5/5 mg/kg (fully effective dose in the mousepox model)
e. P-value is not significant at the one-sided alpha of 0.0125.

Safety

ADVERSE EVENTS

Common Adverse Reactions: The most common adverse reactions (adverse events assessed as causally related by the investigator) experienced in the first 2 weeks of dosing with Tembexa® were diarrhea and nausea. Adverse reactions that occurred in at least 2% of subjects in the Tembexa® treatment group are shown in Table 2.

Table 2: Adverse Reactions (All Grades) Reported in ≥2% of Subjects

Adverse Reaction	Tembexa® 200 mg N=392 %	Placebo N=208 %
Diarrhea[a]	8	3
Nausea	5	1

Vomiting[b]	4	1
Abdominal pain[c]	3	2

Note: Only adverse reactions with onset in the first 2 weeks of treatment are presented.

a. Composite term includes: bowel movement irregularity, defecation urgency, diarrhea, fecal incontinence, and frequent bowel movements.

b. Composite term includes: vomiting and retching.

c. Composite term includes: abdominal discomfort, abdominal distention, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

Adverse Reactions Leading to Discontinuation: Fifteen subjects (4%) had their treatment with Tembexa® discontinued due to adverse reactions. One subject had two adverse reactions; the other subjects had one reaction each. These adverse reactions were diarrhea (n=9), nausea (n=3), vomiting (n=1), enteritis (n=1), ALT increased (n=1) and dyspepsia (n=1).

Less Common Adverse Reactions: Clinically significant adverse reactions that were reported in <2% of subjects (and also occurred in 2 or more subjects) exposed to Tembexa® and at rates higher than in subjects who received placebo are listed below:

- General and administration site: peripheral edema.
- Metabolism and nutrition: decreased appetite.
- Musculoskeletal and connective tissue: muscular weakness.
- Nervous system: dysgeusia.
- Skin and subcutaneous tissue: rash (includes rash, maculo-papular rash, pruritic rash).

Adverse Reactions in Pediatric Subjects: In 23 pediatric subjects aged 7 months to 17 years who received Tembexa® in a randomized, placebo-controlled clinical trial, the adverse reactions and laboratory abnormalities observed with Tembexa® were similar to adults.

WARNINGS & PRECAUTIONS

Increased Risk for Mortality When Used for Longer Duration: Not indicated for use in diseases other than human smallpox. An increase in mortality was observed in a randomized, placebo-controlled Phase 3 trial when Tembexa® was evaluated in another disease. An increased risk in mortality is possible if Tembexa® is used for a duration longer than at the recommended dosage on Days 1 and 8.

Study 301 (CMX001-301) evaluated Tembexa® versus placebo for the prevention of cytomegalovirus infection. A total of 303 subjects received Tembexa® (100 mg twice weekly) and 149 subjects received matching placebo for up to 14 weeks. The primary endpoint was evaluated at Week 24. All-cause mortality at Week 24 was 16% in the Tembexa® group compared to 10% in the placebo group. Safety and effectiveness of Tembexa® have not been established for diseases other than human smallpox disease.

Elevations in Hepatic Transaminases and Bilirubin: Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have been observed, including cases of concurrent increases in ALT and bilirubin. During the first 2 weeks of Tembexa® therapy in 392 subjects, ALT elevations >3x the upper limit of normal were reported in 7% of subjects and bilirubin elevations >2x the upper limit of normal were reported in 2% of subjects; these elevations in hepatic laboratory tests were generally reversible and did not require discontinuation of Tembexa®. Severe hepatobiliary adverse events including hyperbilirubinemia, acute hepatitis, hepatic steatosis, and venoocclusive liver disease have been reported in less than 1% of subjects.

Diarrhea and Other Gastrointestinal Adverse Events: During the first 2 weeks of Tembexa® therapy in 392 subjects, a composite term of diarrhea (all grade, all cause) occurred in 40% of Tembexa®-treated subjects compared with

25% of subjects in the placebo control group. Treatment with Tembexa® was discontinued in 5% of subjects for diarrhea (composite term) compared with 1% in the placebo control group. Additional gastrointestinal (GI) adverse events included nausea, vomiting, and abdominal pain; some of these adverse events required discontinuation of Tembexa®.

Coadminstration with Related Products: Tembexa® should not be co-administered with intravenous cidofovir. Brincidofovir, a lipid-linked derivative of cidofovir, is intracellularly converted to cidofovir.

Embryo-fetal Toxicity: Based on findings from animal reproduction studies, Tembexa® may cause fetal harm when administered to pregnant individuals. Tembexa® administration to pregnant rats and rabbits resulted in embryotoxicity, decreased embryo-fetal survival and/or structural malformations. These effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of Tembexa®. Use an alternative therapy to treat smallpox during pregnancy, if feasible. Perform pregnancy testing in individuals of childbearing potential before initiation of Tembexa®. Advise individuals of childbearing potential to avoid becoming pregnant and to use effective contraception during treatment with Tembexa® and for at least 2 months after the last dose. Advise individuals of reproductive potential with partners of childbearing potential to use condoms during treatment with Tembexa® and for at least 4 months after the last dose.

Carcinogenicity: Tembexa® is considered a potential human carcinogen. Mammary adenocarcinomas and squamous cell carcinomas occurred in rats at systemic exposures less than the expected human exposure based on the recommended dose of Tembexa®.

Male Infertility: Based on testicular toxicity in animal studies, Tembexa® may irreversibly impair fertility in individuals of reproductive potential.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Brincidofovir is a lipid conjugate of cidofovir, an acyclic nucleotide analog of deoxycytidine monophosphate. The lipid conjugate is designed to mimic a natural lipid, lysophosphatidylcholine, and thereby use endogenous lipid uptake pathways. Once inside cells, the lipid ester linkage of brincidofovir is cleaved to liberate cidofovir, which is then phosphorylated to produce the active antiviral, cidofovir diphosphate. Based on biochemical and mechanistic studies using recombinant vaccinia virus E9L DNA polymerase, cidofovir diphosphate selectively inhibits orthopoxvirus DNA polymerase-mediated viral DNA synthesis. Incorporation of cidofovir into the growing viral DNA chain results in reductions in the rate of viral DNA synthesis.

Dose & Administration

ADULTS

- 10 to <48 kg: 4 mg/kg once weekly for 2 doses (days 1 and 8).
- ≥48 kg: 200 mg once weekly for 2 doses (days 1 and 8).

PEDIATRICS

- <10 kg: Oral suspension: Oral: 6 mg/kg once weekly for 2 doses (on day 1 and day 8).
- 10 to <48 kg: Oral suspension: Oral: 4 mg/kg once weekly for 2 doses (on day 1 and day 8).
- ≥48 kg: Oral suspension or tablet: Oral: 200 mg once weekly for 2 doses (on day 1 and day 8).

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Tablets: 100 mg
- Oral Suspension: 10 mg/mL