PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTEMBEXA®

Brincidofovir tablets

Tablets, 100 mg, Oral

Brincidofovir oral suspension

Suspension, 10 mg/mL, Oral

Professed

Pharmacological classification: Antiviral

ATC Code: J05AB17

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR ADULT AND PEDIATRIC PATIENTS FOR TREATMENT OF SMALLPOX DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS."

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR ADULT AND PEDIATRIC PATIENTS FOR TREATMENT OF SMALLPOX DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS."

1 INDICATION

TEMBEXA (brincidofovir) is indicated for the treatment of human smallpox disease in adult and pediatric patients, including neonates.

Limitations of Use:
TEMBEXA is not indicated for the treatment of diseases other than human smallpox disease.

1.1 Pediatrics

Pediatrics (<18 years of age): Health Canada has authorized an extraordinary use indication for pediatric patients aged <18 years. Pharmacokinetic simulation was used to derive the dosing regimens of TEMBEXA in pediatric patients that are predicted to be comparable to adult exposure from the recommended dose of TEMBEXA [see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics].

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use of TEMBEXA in the geriatric population is not associated with differences in safety [see 7.1.4 Geriatrics].

2 CONTRAINDICATIONS

TEMBEXA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

An increase in mortality was observed in comparison to placebo when TEMBEXA was evaluated in patients who were treated for longer durations (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- TEMBEXA should be avoided in pregnant women or in individuals of childbearing potential who think they might be pregnant. Alternative therapies should be used if possible [see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnancy].
- Perform pregnancy testing in individuals of childbearing potential before initiation of TEMBEXA [see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnancy].
- Perform hepatic laboratory testing in all patients before starting TEMBEXA and while receiving

TEMBEXA, as clinically appropriate.

- Advise women 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 [see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential; Contraception].
- Advise male patients of reproductive potential with female partners of childbearing potential to use condoms during treatment with TEMBEXA and for at least 4 months after the last dose [see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential; Contraception].
- TEMBEXA efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models [see 7 WARNINGS AND PRECAUTIONS, Immune].
- Animal studies have indicated that co-administration of TEMBEXA at the same time as the live smallpox vaccine (vaccinia virus) may reduce the immune response to the vaccine. The clinical impact of this is unknown [see 7 WARNINGS AND PRECAUTIONS, Immune].

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of TEMBEXA in pediatric and adult patients is displayed in Table 1.

Table 1: Recommended Dosage in Pediatric and Adult Patients

Patient's Weight (kg)	TEMBEXA Oral Suspension (10 mg/mL)	TEMBEXA Tablet (100 mg)
Less than 10 kg	6 mg/kg once weekly for 2 doses (on Days 1 and 8)	N/A
10 kg to less than 48 kg	4 mg/kg once weekly for 2 doses (on Days 1 and 8)	N/A
48 kg and above	200 mg (20 mL) once weekly for 2 doses (on Days 1 and 8)	200 mg (two 100 mg tablets) once weekly for 2 doses (on Days 1 and 8)

Patients with Renal Impairment:

No dosage adjustment of TEMBEXA is required for patients with mild, moderate, or severe renal impairment or patients with end stage renal disease (ESRD) receiving dialysis [see 10 CLINICAL PHARMACOLOGY].

Patients with Hepatic Impairment:

Perform hepatic laboratory testing in all patients before starting TEMBEXA and while receiving TEMBEXA, as clinically appropriate. No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) [see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, and 10 CLINICAL PHARMACOLOGY].

4.3 Reconstitution

Not applicable.

4.4 Administration

Avoid direct contact with broken or crushed tablets or oral suspension. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water [see 7 WARNINGS AND PRECAUTIONS and 12 SPECIAL HANDLING INSTRUCTIONS].

TEMBEXA Tablets

TEMBEXA tablets can be taken on an empty stomach or with a low-fat, low calorie meal (approximately 300 calories, with approximately 5% calories from fat). Swallow TEMBEXA tablets whole. Do not crush, break, or divide TEMBEXA tablets.

TEMBEXA Oral Suspension

Take TEMBEXA oral suspension on an empty stomach. Shake oral suspension before use. Use an appropriate oral dosing syringe to correctly measure the total prescribed dose. Discard unused portion after completion of 2 prescribed doses.

For patients who cannot swallow, TEMBEXA oral suspension can be administered by enteral tube (naso-gastric or gastrostomy tubes) as follows:

- Draw up prescribed dose with a calibrated catheter-tip syringe and utilize this syringe to administer the dose via the enteral tube.
- Refill the catheter-tip syringe with 3 mL of water, shake, and administer the contents via the enteral tube.
- Flush the enteral tube with water before and after enteral administration.

4.5 Missed Dose

If you miss the second and final dose of TEMBEXA, take it as soon as possible.

5 OVERDOSAGE

There is no clinical experience with overdosage of TEMBEXA. In the event of an overdose, monitor patients for adverse effects and provide appropriate supportive care.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 100 mg	Colloidal Silicon Dioxide, Crospovidone, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Purified Water, Silicified Microcrystalline Cellulose, Talc and Titanium Dioxide.
	Oral suspension, 10 mg/mL	Citric Acid Anhydrous, Lemon Lime Flavor, Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium, Purified Water, Simethicone 30% Emulsion, Sodium Benzoate, Sucralose, Trisodium Citrate Anhydrous, and Xanthan Gum.

TEMBEXA Tablets:

TEMBEXA tablets are blue modified-oval shaped, coated tablets debossed with “BCV” on one side and “100” on the other side and packaged into blister cards. Each blister cavity contains one film-coated tablet containing 100 mg of brincidofovir. The blister card is placed in a wallet. Each wallet contains one (1) blister card with a total of 4 film-coated tablets.

TEMBEXA Oral Suspension:

TEMBEXA oral suspension is an aqueous based, preserved white to off-white opaque, lemon lime flavored suspension containing 10 mg/mL of brincidofovir packaged into a high-density polyethylene bottle with a low-density polyethylene press-in bottle adaptor (PIBA) inserted into the bottle. Each bottle is filled to deliver 65 or 45 mL of TEMBEXA oral suspension.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

The efficacy 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 drug’s efficacy is not ethical. The efficacy of TEMBEXA is based solely on efficacy studies in animal models of orthopoxvirus disease [see 14 CLINICAL TRIALS].

TEMBEXA should not be used for the treatment of other diseases besides human smallpox disease.

Increased Risk for Mortality When Used for Longer Durations

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. In Study 301 (CMX001-301), 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.

Carcinogenesis and Mutagenesis

TEMBEXA is considered a potential human carcinogen based on findings from animal studies in which rats administered TEMBEXA developed adenocarcinomas and carcinomas. These effects occurred at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA [see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dose Adjustment and 16 NON-CLINICAL TOXICOLOGY].

Do not divide, break, or crush TEMBEXA tablets. Avoid direct contact with broken or crushed tablets or oral suspension. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water [see 12 SPECIAL HANDLING INSTRUCTIONS].

Gastrointestinal

During the first 2 weeks of TEMBEXA therapy in Phase 2 and 3 randomized, placebo-controlled clinical trials in 392 adult patients, 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 [see 8 ADVERSE REACTIONS].

Monitor patients for GI adverse events including diarrhea and dehydration, provide supportive care, and if necessary, do not give the second and final dose of TEMBEXA.

Hepatic/Biliary/Pancreatic

Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have been observed, including cases of concurrent increases in ALT and bilirubin. Severe hepatobiliary adverse events including hyperbilirubinemia, acute hepatitis, hepatic steatosis, and veno-occlusive liver disease have been reported in less than 1% of subjects. During the first 2 weeks of TEMBEXA therapy in Phase 2 and 3 randomized, placebo-controlled clinical trials in 392 adult patients, 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 [see 8 ADVERSE REACTIONS]. Similar, reversible elevations in hepatic enzymes were also observed in rats and monkeys administered brincidofovir [see 16 NON-CLINICAL TOXICOLOGY]. Severe hepatobiliary adverse events including hyperbilirubinemia, acute hepatitis, hepatic steatosis, and veno-occlusive liver disease have been reported in less than 1% of subjects.

Perform hepatic laboratory testing in all patients before starting TEMBEXA and while receiving TEMBEXA, as clinically appropriate. Monitor patients who develop abnormal hepatic laboratory tests during TEMBEXA therapy for the development of more severe hepatic injury. Consider discontinuing TEMBEXA if ALT levels remain persistently >10x the upper limit of normal. Do not give the second and final dose of TEMBEXA on Day 8 if ALT elevation is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or International Normalized Ratio (INR) [see 8 ADVERSE REACTIONS].

Immune

TEMBEXA efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models.

Animal studies have indicated that co-administration of TEMBEXA at the same time as the live smallpox

vaccine (vaccinia virus) may reduce the immune response to the vaccine. The clinical impact of this is unknown.

There are limited data available regarding the co-administration of TEMBEXA with the replication-defective smallpox vaccine (modified vaccinia virus Ankara strain).

Renal

The pharmacokinetics of brincidofovir was not significantly different in subjects with severe renal impairment or ESRD compared with subjects with normal renal function. The pharmacokinetics of the cidofovir metabolite was significantly higher in subjects with severe renal impairment and subjects with ESRD compared with normal subjects, indicating higher exposure to cidofovir. Subjects with ESRD should be on dialysis or other renal replacement therapy during treatment to decrease the potential for accumulation of cidofovir.

Reproductive Health: Female and Male Potential

- **Fertility**

  TEMBEXA may irreversibly impair fertility in males based on findings from animal studies in which brincidofovir induced significant testicular toxicity that presented as a decrease in organ weight, atrophy of the seminiferous tubules, and reduced sperm production and motility. These effects occurred in monkeys and rats at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA [see 16 NON-CLINICAL TOXICOLOGY].

  No fertility studies in women or men have been conducted. Therefore, the risk of irreversible male infertility with the two doses of TEMBEXA is unknown.

- **Individuals of Childbearing Potential**

  Advise women 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 male patients of reproductive potential with female partners of childbearing potential to use condoms during treatment with TEMBEXA and for at least 4 months after the last dose [see 4 DOSAGE AND ADMINISTRATION, 4.1 Dosage Considerations].

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on the use of TEMBEXA in pregnant individuals. TEMBEXA may cause fetal harm when administered to pregnant individuals based on findings from animal reproduction studies and should not be used in pregnant individuals, in individuals who think they might be pregnant, or in women of childbearing age not using contraception. Alternative therapies should be used if possible.

In animal fertility and early embryonic development studies, administration of brincidofovir to pregnant rats and rabbits resulted in embryotoxicity, decreased embryo-fetal survival, and/or structural malformations. These teratogenic effects occurred in animals at systemic exposures less than the expected human exposure based on the recommended dose of TEMBEXA. Additional studies in pregnant rats demonstrated that there was considerable fetal exposure to the brincidofovir metabolite cidofovir in utero and rats born to females administered brincidofovir demonstrated reproductive toxicity into adulthood, including testicular defects in males and reduced litter sizes in females [see 16 NON-CLINICAL TOXICOLOGY].

7.1.2 Breast-feeding

Because of the potential for variola virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended in patients with smallpox. Patients with smallpox should be advised not to breastfeed.

There are no data on the presence of TEMBEXA in human milk, the effects of the drug on the breastfed infant, or on milk production. Precaution should be exercised because many drugs can be excreted in human milk.

When brincidofovir was administered to lactating rats, brincidofovir and, to a greater extent, cidofovir were detected in maternal milk but not in the plasma of nursing pups.

7.1.3 Pediatrics

As in adults, the effectiveness of TEMBEXA in smallpox infected pediatric patients, including neonates, is based solely on efficacy studies in animal models of orthopoxvirus disease. The recommended pediatric dosing regimen is expected to produce brincidofovir exposures that are comparable to those in adults based on a population pharmacokinetic modeling and simulation approach. The dosage for pediatric patients is based on weight.

There have been 23 pediatric subjects aged 7 months to 17 years who received TEMBEXA in a randomized, placebo-controlled clinical trial. The safety of TEMBEXA in adults and in pediatric subjects who received the 4 mg/kg dose were similar [see 8 ADVERSE REACTIONS]. An additional 166 pediatric subjects aged 3 months to 18 years received TEMBEXA from uncontrolled studies and expanded access.

There is no safety data available for pediatric patients weighing <10 kg at the 6 mg/kg dose. Considering the potential effects of physiological immaturity on TEMBEXA pharmacokinetics and because safety has not been established in neonates, caution is advised for use of TEMBEXA in neonates. Monitoring for adverse events, particularly for bilirubin elevations is recommended.

7.1.4 Geriatrics

The nature and severity of adverse events was comparable between subjects older and younger than 65 years. No alteration of dosing is recommended for patients ≥65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of TEMBEXA has not been studied in patients with smallpox disease.

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Elevations in hepatic transaminases and bilirubin have been observed in clinical trials of TEMBEXA including cases of concurrent increases in ALT and bilirubin and ALT elevations >3x the upper limit of normal. Some events required discontinuation of TEMBEXA [see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions].
- Diarrhea and other GI adverse events including severe events, have been observed in clinical trials of TEMBEXA. Some events required discontinuation of TEMBEXA [see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions].

8.2 Clinical Trial Adverse Reactions

The safety of TEMBEXA was evaluated in Phase 2 and 3 randomized, placebo-controlled clinical trials in 392 adult patients aged 18 to 77 years. Of the patients who received a 200 mg total weekly dose of TEMBEXA, 54% were male, 85% were White, 7% were Black/African American, 6% were Asian, and 10% were Hispanic or Latino. Twenty-one percent of patients in the studies were age 65 or older. Of these 392 patients, 85% received a 200 mg total weekly dose of TEMBEXA for at least 2 weeks.

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 in adult patients were diarrhea and nausea. Adverse reactions that occurred in at least 1% of subjects in the TEMBEXA treatment group are shown in Table 3.

Table 3: Adverse Reactions (All Grades) Reported in ≥1% 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
Decreased appetite	1	0
Rash[d]	1	0

Note: Only adverse reactions that had onset within the first 2 weeks of treatment are presented.

a. The diarrhea composite term included the following: bowel movement irregularity, defecation urgency, diarrhea, fecal incontinence, and frequent bowel movements.
b. The vomiting composite term included the following: vomiting and retching.
c. The abdominal pain composite term included the following: abdominal discomfort, abdominal distention, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.
d. The rash composite term included the following: rash, rash maculo-papular, rash pruritic, and erythema.

Adverse Reactions Leading to Discontinuation of TEMBEXA

Fifteen subjects (4%) had their treatment with TEMBEXA discontinued due to adverse reactions. One subject had 2 adverse reactions; the other subjects had 1 adverse reaction each. These adverse reactions were:

- Diarrhea (n=9)
- Nausea (n=3)
- Vomiting (n=1)
- Enteritis (n=1)
- ALT increased (n=1)
- Dyspepsia (n=1)

These adverse reactions were mild (Grade 1, n=1), moderate (Grade 2, n=7), or severe (Grade 3, n=8) in severity and resolved upon discontinuation with TEMBEXA.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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. The most common adverse reaction experienced in the first 2 weeks of dosing with TEMBEXA was diarrhea, which was experienced by 5 pediatric subjects (22%) [see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations].

No safety data is available for pediatric subjects receiving the 6 mg/kg TEMBEXA dose.

8.3 Less Common Clinical Trial Adverse Reactions

Clinically significant adverse reactions that were reported in <1% of subjects (and 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
- Musculoskeletal and connective tissue: muscular weakness
- Nervous system: dysgeusia

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

In the controlled pediatric population (n=23), there were no adverse reactions besides diarrhea that occurred in 2 or more TEMBEXA-treated subjects and at a higher rate than in placebo-treated subjects [see 8 ADVERSE EFFECTS, 8.2.1 Clinical Trial Adverse Reactions – Pediatrics].

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected treatment-emergent laboratory values occurring during the first 2 weeks of treatment with TEMBEXA are presented in Table 4.

Table 4: Frequencies of Selected Laboratory Abnormalities

Laboratory Parameter Abnormality[a]		TEMBEXA 200 mg N=392	Placebo N=208
Alanine aminotransferase (ALT)[b]	n	382	203
	Grade 2 (>3 to 5x ULN), (%)	3	2
	Grade 3 (>5 to 20x ULN), (%)	2	1
	Grade 4 (>20x ULN), (%)	0	0
Aspartate aminotransferase (AST)[c]	n	380	201
	Grade 2 (>3 to 5x ULN), (%)	2	1
	Grade 3 (>5 to 20x ULN), (%)	1	0
	Grade 4 (>20x ULN), (%)	0	0
Total bilirubin	n	382	203
	Grade 2 (>1.5 to 3x ULN), (%)	3	2
	Grade 3 (>3 to 10x ULN), (%)	1	<1
	Grade 4 (>10x ULN), (%)	0	0
Serum creatinine	n	383	205
	Grade 2 (>1.5 to 3x ULN), (%)	4	4
	Grade 3 (>3 to 6x ULN), (%)	<1	0
	Grade 4 (>6x ULN), (%)	0	0

a. Frequencies were based on treatment-emergent laboratory abnormalities and were graded per CTCAE version 4.03 toxicity grading criteria.

b. ALT >10x ULN occurred in 1 subject in the TEMBEXA group and no subjects in the placebo group.
c. No subjects reported AST >10x ULN.

8.5 Post-Market Adverse Reactions

None.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

None.

9.2 Drug Interactions Overview

TEMBEXA should not be co-administered with intravenous cidofovir. Brincidofovir, a lipid-linked derivative of cidofovir, is intracellularly converted to cidofovir [see 10 CLINICAL PHARMACOLOGY].

In Vitro Studies:

Brincidofovir was studied in vitro and found to be a direct and reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP4F2. Brincidofovir was not an inducer of CYP1A2, CYP2B6, or CYP3A. Brincidofovir is an inhibitor of Breast Cancer Resistance Protein (BCRP), Multidrug Resistance-Associated Protein 2 (MRP2), Bile Salt Export Pump (BESP), Organic Anion Transporting Polypeptide 1B1 (OATP1B1), Organic Anion Transporter 1 (OAT1), and OAT3. Brincidofovir is not an inhibitor of OATP1B3, Organic Cation Transporter 2 (OCT2), Multidrug and Toxin Extrusion protein 1 (MATE1), or MATE2-K in vitro.

Clinical Studies:

OATP1B1 and 1B3 Inhibitors: A single 600 mg oral cyclosporine (OATP1B1 and 1B3 inhibitor) dose, co-administered with 100 mg brincidofovir increased the mean brincidofovir AUC0-inf and Cmax by 474% and 369%, respectively.

CYP Substrates: No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) were observed when administered concomitantly with TEMBEXA.

P-gp Substrates: No clinically significant differences in the pharmacokinetics of dabigatran etexilate (P-gp substrate) were observed when administered concomitantly with TEMBEXA.

9.3 Drug-Behavioural Interactions

No studies have been performed with TEMBEXA to evaluate drug-behavioural interactions, including the effects of TEMBEXA on alcohol consumption, sexual activity, or smoking.

9.4 Drug-Drug Interactions

Effect of Other Drugs on TEMBEXA

Concomitant use of TEMBEXA with OATP1B1 and 1B3 inhibitors (clarithromycin, cyclosporine, erythromycin, gemfibrozil, human immunodeficiency virus [HIV] and hepatitis C virus [HCV] protease inhibitors, rifampin [single dose]) increase brincidofovir AUC and C_{max} which may increase TEMBEXA-associated adverse reactions [see 10 CLINICAL PHARMACOLOGY].

Where possible, consider alternative medications that are not OATP1B1 or 1B3 inhibitors. If concomitant use with TEMBEXA is necessary, increase monitoring for adverse reactions associated with TEMBEXA (elevations in transaminases and bilirubin, diarrhea, or other GI adverse events) and postpone the dosing of OATP1B1 or 1B3 inhibitors for at least 3 hours after TEMBEXA administration.

Caution should be used when administering TEMBEXA to patients using functional inhibitors of acid sphingomyelinase (FIASMAs). In vitro, a decrease in ASM activity by FIASMAs was associated with a reduction in cidofovir and cidofovir diphosphate formation; the clinical relevance of this finding is unknown. In patients concomitantly using FIAMSAs and OATP1B1 inhibitors (e.g., cyclosporine), increases in brincidofovir AUC and Cmax were observed [see 10 CLINICAL PHARMACOLOGY].

9.5 Drug-Food Interactions

In a food-effect study, following administration of a 200 mg dose of brincidofovir 100 mg tablets under low fat, low calorie fed conditions, there was a decrease in AUC_T and AUC_I and C_{max} by 26%, 31% and 32%, respectively when compared to administration under fasting conditions. There was a decrease in AUC_T and AUC_I and C_{max} by 33%, 45% and 50%, respectively when a 200 mg dose of the brincidofovir 100 mg tablets (UPM) where administered under moderate fat, moderate calorie fed conditions compared to administration under fasting conditions. No clinically meaningful changes in intracellular concentrations of cidofovir diphosphate were observed. The effect of food on TEMBEXA oral suspension has not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism 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 [see 15 MICROBIOLOGY].

10.2 Pharmacodynamics

Cardiac Electrophysiology

TEMBEXA does not prolong the QT interval at the anticipated therapeutic exposure.

10.3 Pharmacokinetics

Brincidofovir is a prodrug that is converted intracellularly to cidofovir, which is subsequently phosphorylated to cidofovir diphosphate, the active antiviral moiety, following oral administration.

Brincidofovir plasma exposures do not accumulate after repeat doses. The metabolite cidofovir diphosphate reaches maximum concentration at 47 hours (23 to 311 hours) following administration of the recommended dose, with a mean (CV%) half-life of 113 hours (34.2%). The pharmacokinetic properties of brincidofovir following administration are provided in Table 5. The pharmacokinetic parameters of brincidofovir and cidofovir diphosphate following administration of TEMBEXA at the recommended dose are provided in Table 6.

Table 5: Pharmacokinetic Properties of Brincidofovir[a]

Absorption		
Bioavailability	Oral suspension	16.8%
	Tablet	13.4%
T_{max}[b]		3 hours (2 to 8 hours)
Distribution		
% Bound to human plasma proteins		>99.9%
Blood-to-plasma ratio (drug or drug-related materials)[d]		0.48 to 0.61
Apparent Volume of distribution, L		1230
Elimination		
Apparent Clearance, L/hr		44.1
Mean terminal half-life ($t_{1/2}$), hr		19.3
Metabolism		
Metabolic pathways[d]		hydrolysis, CYP4F2
Metabolites		cidofovir and cidofovir diphosphate (active)
Excretion		
% of dose excreted in urine[c]		51%, as metabolites
% of dose excreted in feces[c]		40%, as metabolites

a. Healthy adults.
b. Administered under fasted conditions.
c. Following administration of radiolabeled brincidofovir.
d. One enzyme involved in brincidofovir hydrolysis is acid sphingomyelinase.

Table 6: Single-Dose Pharmacokinetic Parameters of Brincidofovir and Cidofovir Diphosphate[a]

	Geometric Mean (%CV)	
PK Parameter	**Brincidofovir**	**Cidofovir diphosphate**
C_{max}	480 ng/mL (70%)	9.7 pg/10^6 cells (75%)
AUC_{tau}	3400 ng·hr/mL (58%)	1200 pg·hr/10^6 cells (75%)

AUC = area under the time concentration curve; Cmax = maximum concentration; CV = coefficient of variation.
a. Healthy adults

Brincidofovir is metabolized by hydrolysis of the phosphoester bond to form cidofovir. Cidofovir is subsequently phosphorylated to form cidofovir diphosphate. Brincidofovir is also carboxylated at the terminal carbon by Cytochrome P450 (CYP) 4F2, followed by subsequent CYP-mediated oxidations and multiple cycles of fatty acid beta-oxidation. The major inactive metabolites formed via these pathways are CMX103 (3-hydroxypropyl ester of cidofovir) and CMX064 (4-(3-propoxy)butanoic acid ester of cidofovir).

Genetic and chemical inhibition of acid sphingomyelinase enzyme activity in multiple human cell lines resulted in substantially lower concentrations of cidofovir and cidofovir diphosphate (the active drug), compared to controls with functional acid sphingomyelinase enzyme activity. Findings show acid sphingomyelinase plays a major role in the hydrolysis of brincidofovir to cidofovir in these cell lines.

Based on in vitro data, acid sphingomyelinase deficiency may reduce the ability to convert brincidofovir to cidofovir and cidofovir diphosphate; however, the clinical relevance of this finding is unknown.

Comparison of Animal and Human Pharmacokinetic Data to Support Effective Human Dose Selection

Because the effectiveness of TEMBEXA against variola virus cannot ethically be tested in humans, a comparison of brincidofovir and cidofovir diphosphate exposures achieved in human subjects to those observed in animal models of orthopoxvirus infection (rabbits infected with rabbitpox virus, and mice infected with ectromelia virus) in efficacy studies was necessary to support the dose and regimen of 200 mg once a week for 2 doses for the treatment of smallpox disease in adults. Humans achieve greater systemic exposures (AUC and C_{max}) of brincidofovir and greater than or equal to intracellular concentrations of cidofovir diphosphate following a 200 mg once a week dose when compared with therapeutic exposure in the animal models [see 14 CLINICAL TRIALS].

Special Populations and Conditions

No clinically meaningful differences in the pharmacokinetics of TEMBEXA were observed based on age, sex, race, reduced activity of CYP4F2 enzyme, renal impairment including ESRD with or without dialysis (based on estimated glomerular filtration rate [GFR]), or hepatic impairment (Child-Pugh Class B, C).

Pediatrics

The pharmacokinetics of TEMBEXA following oral suspension administrations has been evaluated in pediatric patients with non-orthopox viral diseases (n=218, 4 months to 18 years of age). Pharmacokinetic simulation was used to derive the dosing regimen and it was predicted to provide pediatric patients with exposures comparable to the observed exposure in adults receiving 200 mg TEMBEXA tablets. Considering *the* potential effects of physiological immaturity on TEMBEXA pharmacokinetics and because safety has not been established in neonates receiving the 6 mg/kg dose, caution is advised for use of TEMBEXA in neonates. Monitoring for adverse events, particularly for bilirubin elevations is recommended.

Hepatic Insufficiency

Compared to subjects with normal hepatic function, exposure (AUCinf) in subjects with severe hepatic impairment was 30% higher compared to subjects with normal hepatic function following a single 200 mg dose of brincidofovir.

Renal Insufficiency

Following a single oral dose of 100 mg brincidofovir, there were no meaningful differences in exposure in patients with mild, moderate, and severe renal impairment compared to subjects with normal renal function. Subjects with ESRD (pre-hemodialysis) had 1.6-fold higher exposure (AUClast) compared to subjects with normal renal function. The exposure to cidofovir was greatly increased with severe renal impairment and ESRD. Subjects with severe renal impairment experienced an approximately 5-fold increase in Cmax and roughly 12-fold increase in AUC. Subjects with ESRD had roughly 10-fold increases in Cmax and a 25-fold increase in AUClast compared to that in subjects with normal renal function.

11 STORAGE, STABILITY AND DISPOSAL

TEMBEXA Tablets:

Store at room temperature (15°C to 30°C)

TEMBEXA Oral Suspension:

Store at room temperature (15°C to 30°C). Do not freeze.

12 SPECIAL HANDLING INSTRUCTIONS

TEMBEXA Tablets:

Do not divide, break, or crush TEMBEXA tablets. Avoid direct contact with broken or crushed tablets. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.

TEMBEXA Oral Suspension:

Avoid direct contact with TEMBEXA oral suspension. If contact with skin or mucous membranes occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with water.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

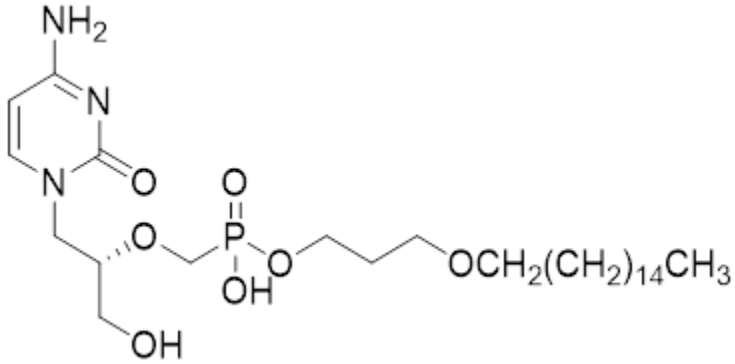
Proper/Common name: brincidofovir

Chemical name: The full chemical name of brincidofovir is Phosphonic acid, *P*-[[(1*S*)-2-(4-amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-, mono[3-(hexadecyloxy)propyl] ester.

Molecular formula: $C_{27}H_{52}N_3O_7P$

Molecular mass: 561.70.

Structural formula:



Physicochemical properties: Brincidofovir is a white to off-white crystalline powder as a free acid, polymorphic form (Form II) and practically insoluble in water.

14 CLINICAL TRIALS

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR ADULT AND PEDIATRIC PATIENTS FOR TREATMENT OF SMALLPOX DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS."

14.1 Trial by Indication

Treatment of Smallpox

The effectiveness of TEMBEXA for the 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 non-variola orthopoxviruses, which cause severe disease and mortality in the immunocompetent animals used for these studies. 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 strain Utrecht) and the mousepox model (BALB/c mice infected with ectromelia virus strain Moscow).

In the rabbitpox study, rabbits were lethally challenged intradermally with 600 plaque-forming units of rabbitpox virus strain Utrecht; 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 strain Moscow; brincidofovir was administered orally (every 48 hours for 3 doses) with a treatment regimen of 20/5/5 mg/kg initiated on 4-, 5-, 6-, or 7-days post challenge or a treatment regimen of 10/5/5 mg/kg initiated on 4-, 5-, or 6-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.

14.2 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 7).

Table 7: Survival Rates in Brincidofovir Treatment Studies in the Rabbitpox and Mousepox Models

Animal Model Dose Regimen	Treatment Initiation Day	Survival % (# survived/n)		Survival Rate Difference (95% CI)[a]	p-value[b]
		Placebo	Brincidofovir		
Rabbitpox[c]					
20/5/5 mg/kg	Day 3	29% (8/28)	100% (29/29)	71% (51%, 87%)	<0.0001
	Day 4		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]					
10/5/5 mg/kg	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]
20/5/5 mg/kg	Day 4		84% (27/32)	72% (50%, 87%)	<0.0001
	Day 5		75% (24/32)	63% (40%, 79%)	<0.0001
	Day 6		47% (15/32)	34% (11%, 55%)	0.0014
	Day 7		38% (12/32)	25% (3%, 46%)	0.0118

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.

15 MICROBIOLOGY

Activity in Cell Culture

The median 50% effective concentration (EC_{50}) of brincidofovir against variola virus was 0.11 µM (range 0.05 to 0.21 µM) across 5 variola virus strains chosen to represent 5 distinct variola virus DNA polymerase genotypes.

Resistance

There are no known instances of naturally occurring brincidofovir resistant orthopoxviruses, although brincidofovir resistance may develop under drug selection. Cell culture studies have shown that certain amino acid substitutions in the target viral DNA polymerase protein can confer reductions in brincidofovir antiviral activity. The possibility of resistance to brincidofovir should be considered in patients who either fail to respond to therapy or who develop recrudescence of disease after an initial period of responsiveness.

Cross-resistance

Cross-resistance between brincidofovir and tecovirimat is not expected based on their distinct mechanisms of action. Where tested, orthopoxvirus isolates resistant to tecovirimat have not been resistant to brincidofovir and/or cidofovir and vice versa.

16 NON-CLINICAL TOXICOLOGY

General Toxicity:

Gastrointestinal Toxicity: In single dose studies performed in rats and repeat daily dosing studies (14 days) performed in mice and monkeys, orally-administered brincidofovir resulted in gastropathy, enteritis and/or enteropathy, the extent of which was dose-dependent. In surviving animals, this was characterized by reversible absent/liquid/soft feces production, dehydration, decreased body weight, and reduced food consumption.

Brincidofovir doses that induced gastrointestinal toxicity produced systemic exposures of brincidofovir that were equivalent to or lower than the expected clinical systemic exposure. Oral administration of brincidofovir twice weekly in monkeys and rats, to reflect intended clinical use, attenuated gastrointestinal toxicity such that incidences were limited to small, reversible reductions in body weight/food intake and few, sporadic reports of reversible soft feces production. Intravenous administration of brincidofovir in rats increased systemic exposures and was associated with single cell intestinal crypt epithelia necrosis.

Hepatic and Renal Toxicity: Single dosing of rats with 300 mg/kg brincidofovir via oral gavage induced 2- to 4-fold increases in the blood concentration of ALT and alkaline phosphatase. In addition, monkeys administered brincidofovir via oral gavage either once daily for 14 days (4 mg/kg) or twice weekly for up to 39 weeks (4 to 15 mg/kg) exhibited 2- to 5-fold elevations in blood concentration of ALT and AST. Renal tubular epithelial karyomegaly was observed when brincidofovir was administered to monkeys twice weekly for up to 39 weeks. These hepatic and renal observations were reversible after the dosing period and not associated with any other tissue abnormalities.

Carcinogenicity:

Palpable masses occurred in rats with high frequency after biweekly dosing for 13 weeks with ≥1 mg/kg brincidofovir at systemic exposures less than the expected human exposure based on the

recommended dose of TEMBEXA. The masses diagnosed as mammary adenocarcinomas, carcinoma in squamous cell, Zymbal's gland, uterus, and small intestine and hemangiosarcomas in mesenteric and mediastinal lymph node, liver and abdominal cavity were observed in rats following long term (13-weeks and 26-weeks) dosing studies. No tumors occurred in rats after 9 twice-weekly intravenous doses, although rats were only followed for 14 days after the last administration. Based on these data and the unknown translation of nonclinical findings to clinical risk, brincidofovir is considered a potential human carcinogen.

Genotoxicity:

Brincidofovir was negative in a bacterial mutagenicity (Ames) assay and an in vivo micronucleus assay in mice. Brincidofovir was positive for increased structural chromosomal aberrations in the absence of metabolic activation in an in vitro assay.

Reproductive and Developmental Toxicology:

In chronic dosing studies with orally administered brincidofovir, testicular effects were seen in both rats and monkeys. Monkeys administered twice weekly doses of ≥5 mg/kg brincidofovir via oral gavage for 9 months exhibited atrophy of the seminiferous tubules and hypospermia in the epididymides. Based on sperm analysis and histopathology, these findings demonstrated a trend towards recovery after a 6-month, post-dosing period, although observations at the post-dosing period were not consistent across all study groups and limited by a small sample size. Rats administered 15 mg/kg brincidofovir via oral gavage twice weekly for 13 weeks exhibited decreased testes weights, depletion of spermatogenesis and hypospermia. Unlike in the monkey, a trend toward recovery was not demonstrated in rat studies incorporating either a 12-week or 26-week post-dosing period. Reproductive studies demonstrated that these effects of brincidofovir were sufficient to render rats dosed twice weekly by oral gavage >13 weeks infertile.

Brincidofovir exposures in both monkeys and rats were less than exposures seen in humans administered 200 mg TEMBEXA. Studies conducted using intravenous brincidofovir to achieve clinically relevant exposures demonstrated reduced testicular and epididymis weight, germ cell depletion, and seminiferous tubule epithelial apoptosis in rats dosed twice weekly for 1 to 4 weeks, which were non-reversible during the 2-to-6-week recovery period. Testicular toxicity was less pronounced in rats observed 15 weeks after intravenous administration once weekly for 3 weeks with mild testicular tubular atrophy and germ cell depletion limited to a minority of seminiferous tubules.

Brincidofovir was teratogenic when administered to pregnant rats and rabbits once daily at 4.5 mg/kg/day. In addition, in a rat fertility and early embryonic development study, administration of brincidofovir once daily beginning 15 days before cohabitation, during cohabitation, and continuing through gestation day 7 resulted in decreased embryonal viability and litter size at 0.25 mg/kg/day, a dose that did not cause maternal toxicity. Administration of brincidofovir to pregnant female rats caused considerable in utero fetal exposure of the metabolite cidofovir and reproductive toxicity was observed in rats born to females administered brincidofovir that presented in adulthood and included testicular defects in males and reduced litter sizes in females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEMBEXA®

Brincidofovir Tablet

Brincidofovir Oral Suspension

Read this carefully before you start taking **TEMBEXA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEMBEXA**.

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR ADULT AND PEDIATRIC PATIENTS FOR TREATMENT OF SMALLPOX DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS."

Serious Warnings and Precautions

An increase in death was seen when TEMBEXA was studied in patients who were treated for longer periods of time.

See "Other warnings you should know about" for more information.

What is TEMBEXA used for?

TEMBEXA is used to treat smallpox disease in adults, children and infants.

Limitations of Use:

Tembexa is not approved for the treatment of diseases other than smallpox disease.

How does TEMBEXA work?

Smallpox disease is caused by type of virus called variola virus. TEMBEXA is an antiviral medicine that acts against variola virus. It prevents the virus from replicating.

What are the ingredients in TEMBEXA?

Tablet:

Medicinal ingredients: brincidofovir

Non-medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Purified Water, Silicified Microcrystalline Cellulose, Talc and Titanium Dioxide.

Oral Suspension:

Medicinal ingredients: brincidofovir

Non-medicinal ingredients: Citric Acid Anhydrous, Lemon Lime Flavor, Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium, Purified Water, Simethicone 30% Emulsion, Sodium Benzoate, Sucralose, Trisodium Citrate Anhydrous and Xanthan Gum.

TEMBEXA comes in the following dosage forms:

Tablets: 100 mg
Oral Suspension: 10 mg/mL

Do not use TEMBEXA if:

- You are allergic to brincidofovir.
- You are allergic to any of the other ingredients in TEMBEXA or to a component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEMBEXA. Talk about any health conditions or problems you may have, including if you:

- are immunocompromised, which means you have problems with your immune system.
- have kidney problems.
- have recently received or plan to receive a smallpox vaccination.

Other warnings you should know about:

Talk to your doctor or pharmacist before taking TEMBEXA.

Increased risk of death when used for longer periods:

An increase in death was seen when TEMBEXA was studied in patients with another disease. These patients were treated for longer periods of time. An increased risk of death is possible if TEMBEXA is used for longer than the recommended two doses. Therefore, TEMBEXA should only be used as recommended, with one dose on Day 1 and one dose on Day 8.

Liver testing and problems:

Your healthcare professional should perform blood tests to check your liver before you start taking TEMBEXA and while you are taking it. Contact your healthcare professional right away if you have any symptoms of liver problems. These include: stomach pain, right upper stomach area pain or swelling, dark urine, yellowing of your skin or the whites of your eyes, flu like symptoms, swelling of the belly, nausea, vomiting, throwing up of blood, extreme tiredness, confusion, abnormal liver blood testing results provided by your doctor.

Women - Preventing pregnancy:

Before you take TEMBEXA, tell your healthcare professional if you are pregnant, think you might be pregnant, or plan to become pregnant. TEMBEXA can harm your unborn infant. Tell your healthcare provider if you become pregnant or think you may be pregnant while you are taking TEMBEXA.

Your healthcare professional will check to see if you are pregnant before you start taking TEMBEXA.

Your healthcare professional may use another medicine to treat your smallpox disease if you are pregnant. You must use effective birth control while you are taking TEMBEXA and for 2 months after you stop taking it. Talk to your healthcare professional for more information on effective birth control methods.

Men - Preventing pregnancy in female partners and fertility:

TEMBEXA may harm your sperm. If you are sexually active with a woman you must use condoms while you are taking TEMBEXA and for 4 months after you stop taking it. TEMBEXA can also affect your fertility and ability to conceive children. This may not be reversible.

Breastfeeding:

Tell your healthcare professional if you are breastfeeding or plan to breastfeed. You should not breastfeed when you have smallpox disease. This is because of the risk of passing the smallpox virus to your infant through your breastmilk. Before you take TEMBEXA, talk to your healthcare professional on how best to feed your infant while you are taking TEMBEXA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with TEMBEXA

- Cidofovir, used to treat eye infections.
- Medicines called protease inhibitors, used to treat human immunodeficiency virus (HIV) or hepatitis C virus (HCV).
- Clarithromycin, erythromycin and rifampin, antibiotics used to treat infections.
- Gemfibrozil, used to treat heart disease.
- Cyclosporine, used to treat organ rejection in transplant patients.

How to take TEMBEXA:

- Always take TEMBEXA exactly as your healthcare professional has told you.
- Check with your healthcare professional if you are not sure.
- Take TEMBEXA once a week for 2 doses in total (on Day 1 and Day 8).
- Take TEMBEXA tablets on an empty stomach or with a low-fat, low calorie meal (around 300 calories, with approximately 5% calories from fat). Talk to your healthcare professional for examples of foods that you can eat for a low-fat meal.
- Swallow tablet whole with water. Do not crush, break, or divide them.
- Take TEMBEXA oral suspension on an empty stomach.
- Shake the oral suspension bottle well before each use. Use an oral dosing syringe to correctly measure your dose. Ask your pharmacist for an oral dosing syringe if you do not have one. Only take the amount prescribed to you. Throw away any unused portion after completion of 2 prescribed doses.
- **For people who are not able to swallow:** You may give TEMBEXA oral suspension through a naso-gastric or gastrostomy tube to someone who is not able to swallow. Use the following instructions:
  - Draw up the prescribed dose of TEMBEXA oral suspension using a catheter-tip syringe with mL markings on it.
  - Give the dose through the naso-gastric tube or gastrostomy tube.
  - Refill the catheter-tip syringe with 3 mL of water and shake the syringe. Give the contents of the syringe through the naso-gastric tube or gastrostomy tube.
  - Flush with water before and after administration.
- Stay under the care of your healthcare professional during treatment with TEMBEXA.

- If you touch TEMBEXA, wash your hands very well with soap and water. If you get TEMBEXA in your eyes, rinse your eyes well with water.

Usual dose:

The usual dose of TEMBEXA is based on your weight and your ability to swallow tablets. Your healthcare professional will tell you how much TEMBEXA to take.

Overdose:

If you think you, or a person you are caring for, have taken too much TEMBEXA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss the second and final dose of TEMBEXA, take it as soon as possible.

What are possible side effects from using TEMBEXA?

These are not all the possible side effects you may have when taking TEMBEXA. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea
- Diarrhea
- Vomiting
- Decreased appetite
- Rash

Serious side effects of TEMBEXA and what to do about them			
Symptom/effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Common			
Severe Diarrhea: four or more loose or liquid bowel movements in a day.		X	N/A
Uncommon			
Liver problems: stomach pain, right upper stomach area pain or swelling, dark urine, yellowing of your skin or the whites of your eyes, flu like symptoms, swelling of the belly, nausea, vomiting, throwing up of blood, extreme tiredness, confusion, abnormal		X	N/A

liver blood testing results provided by your doctor.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store TEMBEXA tablets and oral suspension at room temperature (15°C to 30°C).
- Do not freeze TEMBEXA oral suspension.

Keep out of reach and sight of children.

If you want more information about TEMBEXA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by calling Emergent BioDefense Operations Lansing LLC at 1-877-246-8472.

This leaflet was prepared by Emergent BioDefense Operations Lansing LLC.
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