Summary of Product Characteristics
BROMSITE

1. NAME OF THE MEDICINAL PRODUCT

Bromsite

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 0.75 mg bromfenac (as sodium sesquihydrate)

3. PHARMACEUTICAL FORM

Ophthalmic solution

4. THARAPEUTIC INDICATION

Bromsite is indicated for the treatment of postoperative inflammation and prevention of ocular pain in adult patients undergoing cataract surgery.

5. DOSAGE AND ADMINISTRATION

5.1 Recommended Dosing

One drop of Bromsite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

5.2 Use with Other Topical Ophthalmic Medications

Bromsite should be administered at least 5 minutes after instillation of other topical medications. Bromsite may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

6. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the inactives listed in section 10.

7. WARNINGS AND PRECAUTIONS

7.1 Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including Bromsite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

7.2 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including Bromsite. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

7.3 Increased Bleeding Time of Ocular Tissue

With some NSAIDs, including Bromsite, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Bromsite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

7.4 Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including Bromsite, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

7.5 Contact Lens Wear

Bromsite should not be administered while wearing contact lenses. The preservative in Bromsite, benzalkonium chloride, may be absorbed by soft contact lenses.

8. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Slow or Delayed Healing [*see Warnings and Precautions (7.1)*]
- Potential for Cross-Sensitivity [*see Warnings and Precautions (7.2)*]
- Increased Bleeding Time of Ocular Tissue [*see Warnings and Precautions (7.3)*]
- Keratitis and Corneal Reactions[*see Warnings and Precautions (7.4)*]
- Contact Lens Wear [*see Warnings and Precautions (7.5)*]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

8.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions in 1-8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

9. USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of Bromsite during late pregnancy should be avoided.

Data

Animal Data

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

9.2 Lactation

There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low [*see Clinical Pharmacology (11.2)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

9.3 Pediatric Use

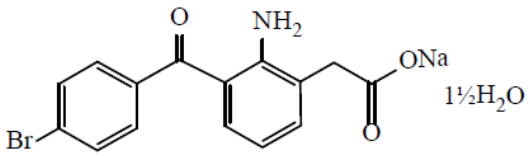
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

9.4 Geriatric Use

There is no evidence that the efficacy or safety profiles for Bromsite differ in patients 65 years of age and older compared to younger adult patients.

10. DESCRIPTION

Bromsite (bromfenac ophthalmic solution) 0.075% is a sterile aqueous, topical NSAID, formulated in DuraSite® for ophthalmic use. The USAN name for bromfenac sodium sesquihydrate is bromfenac sodium. Bromfenac sodium is designated chemically as sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate, with an empirical formula of C15H11BrNNaO3• 1½H2O. The structural formula for bromfenac sodium sesquihydrate is:



Bromfenac sodium is a bright orange to yellow powder. The molecular weight of bromfenac sodium sesquihydrate is 383.17. Bromsite is a greenish-yellow to dark yellow viscous liquid with an osmolality of approximately 290 mOsmol/kg.

Preservative: benzalkonium chloride

Inactives: Polycarbophil, sodium borate, boric acid, sodium chloride, citric acid anhydrous, poloxamer 407, sodium citrate dihydrate, edetate disodium dihydrate, benzalkonium chloride, 2N sodium hydroxide, water for injection.

11. CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

11.2 Pharmacokinetics

Following bilateral topical ocular twice-daily dosing of bromfenac 0.075% ophthalmic solution, the plasma concentrations of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30 to 60 minutes post-dose.

12. NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

13. CLINICAL STUDIES

13.1 Ocular Inflammation and Pain

Clinical efficacy was evaluated in 2 multi-centered, randomized, double-masked, parallel group, placebo-controlled US trials in which subjects requiring cataract surgery were assigned to receive Bromsite or vehicle. Patients undergoing cataract surgery self-administered Bromsite or vehicle twice daily, beginning 1 day prior to surgery, continuing the day of surgery and for 14 days after surgery. Clearance of ocular inflammation was assessed on Days 1, 8, 15, and 29 using slit lamp biomicroscopy. The primary efficacy endpoint was the proportion of subjects with anterior chamber cell (ACC) grade 0 at Day 15. The secondary efficacy endpoint was the proportion of subjects who were pain free after cataract surgery as assessed using a Visual Analog Scale.

Proportion of Subjects with Cleared Ocular Inflammation, ACC Grade 0				
	Visit	BromSite	Vehicle	Treatment Difference (95% CI)
Study 1	Day 8	54/168 (32.1%)	7/85 (8.2%)	23.9% (14.7%, 33.1%)
	Day 15	96/168 (57.1%)	16/85 (18.8%)	38.3% (27.1%, 49.5%)
Study 2	Day 8	40/168 (23.8%)	8/85 (9.4%)	1 4.4% (5.5%, 23.3%)
	Day 15	64/168 (38.1%)	19/85 (22.4%)	1 5.7% (4.2%, 27.3%)
Proportion of Subjects who were Pain Free				
Study 1	Day 1	129/168 (76.8%)	41/85 (48.2%)	28.6% (16.2%, 40.9%)
Study 2	Day 1	138/168 (82.1%)	53/85 (62.4%)	19.8% (8.0%, 31.6%)

14. HOW SUPPLIED/STORAGE AND HANDLING

Bromsite is supplied in low density polyethylene (LDPE) plastic bottles and dropper tips, and high density polyethylene (HDPE) eyedropper caps. Each bottle is provided in a heat-sealed laminated aluminum foil pouch.

2.5ml or 5ml bottle. Not all package size may be marketed.

Storage:

Store at not more than 25ºC. Use within 32 days after first opening.

Manufacturer:

Woodstock Sterile Solutions, Inc, 2210 Lake Shore Drive, Woodstock, IL 60098 USA

Marketing Authorisation holder:

Taro International Ltd., 14 Hakitor St., Haifa Bay 2624761, Israel

Marketing Authorisation number: 166.23.35657

Approved on December 2020