Safety of Bromfenac Formulated in DuraSite® on Ocular Tissues

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Background

- Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) that has potent anti-inflammatory, antipyretic, and analgesic activities.
- Bromfenac like other NSAIDs acts by inhibiting cyclo-oxygenase (COX) in the tissues, thereby blocking or reducing the production of various prostaglandins, which are responsible for various signs and symptoms of inflammation.
- In 2005, a bromfenac formulation gained market approval from the FDA for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
- Ophthalmic formulations containing 0.045% to 0.18% bromfenac formulated in DuraSite® have been developed.
- DuraSite is a polymeric drug delivery system that prolongs drug residence time on the eye.
- DuraSite® formulations of 0.045% and 0.09% bromfenac have previously shown to give high aqueous humor levels over eye drop formulations.

Purpose

The purpose of this study was to investigate the ocular toxicity and safety of bromfenac formulated in DuraSite® across ocular tissues.

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Methods

- Bromfenac was formulated in the DuraSite® vehicle including a vehicle with concentrations of 0.045%, 0.09% and 0.18% preserved with benzalkonium chloride.
- Male and female Dutch-Belted rabbits were assigned to 4 groups (3/sex/group). Group 1 received vehicle control and groups 2, 3, and 4 received ISV-303 at concentrations of 0.045%, 0.09%, or 0.18% respectively.
- One drop of ISV-303 test formulation or vehicle was instilled into the left eye of each animal twice-daily and the right eye served as a control.
- All animals were dosed for a period of 14 days (study days 1–14) and all animals were then sacrificed on study day 15.
- Data evaluated for compound effects included mortality and moribundity, clinical observations, body weights, body weight changes, food consumption, twice-daily macroscopic examinations (before AM and after PM dose administrations), microscopic ophthalmic examination, intraocular pressures, clinical pathology, gross necropsy findings, organ weights, and ocular histopathology.

Results

- No test article related effects were apparent from clinical observations, body weight or body weight change data.
- There were no significant changes in food consumption.
- Macroscopic ocular findings were not toxicologically meaningful. Some animals were observed to have discharge which was also seen in the vehicle control group.
- Ophthalmic examinations during the termination examination showed one male animal was found to have slight fluorescein staining of the right (untreated) eye and showed no suspected test article related findings.
- There were only 2 statistically significant differences in IOPs between untreated and treated eyes during the study. As the magnitude of the differences were small (≤ 2mm Hg), these statistically significant differences have no physiologic significance.
- No differences were observed in serum chemistry in any groups of either pre-dose or terminal phases except the termination chloride value in Group 4 males had a statistically significantly increase; however, it is considered incidental because of lack of correlated abnormalities.
- In the pre-dose phase and terminal visits, the mean corpuscular hemoglobin concentration (MCHC) noted statistical differences. The statistically significant changes noted during the pre-dose phase and terminal phase were considered to be clinically insignificant and incidental variations due to absence of correlated alterations in other clinical pathology parameters.
- Ocular histopathologic examination showed findings that consisted of mild lymphoplasmacytic cellular infiltrate in the palpebral conjunctiva or at the limbus. These findings occurred in nearly equal frequency between the left (treated) and right (untreated) eyes and equally among control and ISV-303 treated animals (groups 2 through 4). The mild lymphoplasmacytic cellular infiltrate was considered incidental and not related to treatment.
- There were no compound-related changes in the necropsy findings or organ weights. At necropsy there were three different types of lesions (pulmonary hemorrhage, irregular cortex in the kidney, and alopecia) were observed; however, no lesion was considered test article-related.

Conclusion

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- Ocular instillation of the DuraSite® eye drop formulation with bromfenac concentrations ranging from 0.045% to 0.18% to Dutch-Belted rabbits twice-daily for 14 days elicited no evidence of ocular irritation or systemic toxicity and no dose-related effects on specific ocular indices (tonometry, macroscopic examination, slit lamp biomicroscopy, ophthalmoscope examination, and ocular histopathology). The NOAEL for ocularly administered bromfenac formulated in DuraSite® to rabbits is considered to be > ~126 µg/eye/day.

References

- Sancilio LF, Nolan JC, Wagner LE, Ward JW, Arzneimittelforschung, 1987 May; 37(5):513-9.
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Author Disclosure Information

All authors are employees of InSite Vision Incorporated.