A New Paradigm in NSAID Treatment

Contents

♦ Common Uses of Ophthalmic NSAIDs
♦ History of Xibrom™ (bromfenac ophthalmic solution) 0.09%
♦ Efficacy of Xibrom™
  • Phase III trials
  • Pain data
  • Post-Approval trials
♦ Pharmacokinetics, Penetration, and Potency
♦ Safety of Xibrom™
  • Oral NSAIDs vs. Ophthalmic NSAIDs
  • Japanese experience and post-approval surveillance data
  • US Pivotal trials

Current Uses of Ophthalmic NSAIDs

♦ Intraoperative miosis
♦ Relief of:
  • Pain
  • Inflammation
  • photophobia
♦ Ocular allergy
♦ Reduction of post-cataract cystoid macular edema (CME)

*Conditions for which bromfenac ophthalmic solution has been studied or for which data are available.

History of Xibrom™

♦ Japan Approval, May 2000:
  • blepharitis, conjunctivitis, scleritis and post-operative inflammation
  • 6 Years & approximately 10.3 million patient uses
  – established track record of efficacy & safety
♦ US Approval, March 2005:
  – same formulation as used in Japan

Published Comparative Papers From Trials in Japan

♦ Inflammation Post-Surgery
  • Significantly less flare in first 14 days for bromfenac (BID) vs. diclofenac (QID)
  • Significantly less AC cells & protein in first 3 days for bromfenac (BID) than diclofenac (TID)
♦ Relief of Seasonal Allergy
  • Bromfenac equal in efficacy to pemirolast
♦ Prevention of Miosis in Cataract Surgery
  • Bromfenac equal in efficacy to diclofenac

2. Data on File, ISTA Pharmaceuticals Inc.

Note: All topical nonsteroidal anti-inflammatory drugs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing.
**Xibrom™**
(bromfenac ophthalmic solution) 0.09%

**Indicated as:**
- the first and only BID dosed NSAID for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction

**Contraindicated:**
- in patients with known hypersensitivity to any ingredient in the formulation

**Most commonly reported adverse experiences:**
- Abnormal sensation in eye, conjunctival hyperemia, eye irritation, eye pain, eye pruritus, eye redness, headache and illtis. These events were reported in 2%-7% of patients

**Effect of BID on Compliance**

*Evaluation and Multivariate Statistical Analysis of Factors Influencing Patient Adherence to Ophthalmic Solutions*

- 71 ophthalmic patients
- Ophthalmology Department at Hiroshima University

**Xibrom™ Phase III Trials: Key Points**
- No pre-surgical dosing of an NSAID
- No anti-inflammatory agent until **ONE DAY** after surgery
- Summed Ocular Inflammation score prior to treatment = 3.7
  - **High level of inflammation for routine cataract procedure**
- Xibrom™: Dosed BID

**Visit & Treatment Schedule**

<table>
<thead>
<tr>
<th>Treatment Evaluation</th>
<th>Days Post-Surgery</th>
<th>Days Post-Treatment Initiation</th>
<th>Approximate Doses of Xibrom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 – Day of Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 – Return to office for Entry Criteria Evaluation (no anti-inflammatory used)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1st) Day 3</td>
<td>2</td>
<td>4-6</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Day 8</td>
<td>7</td>
<td>14-16</td>
</tr>
<tr>
<td>3rd</td>
<td>Day 15</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>4th</td>
<td>Day 22</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>Day 29</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

**Xibrom™ US Phase III Protocol Review**

- Randomized, double masked, placebo-controlled studies
- Similar protocol to ketorolac 0.5% Phase III
- **ONLY** NSAID pivotal trial requiring an end-point of zero

**Xibrom™ US Phase III Trials: Inflammation Reduction: Summed Ocular Inflammation Score**

- Xibrom achieved statistical significance on 1st treatment evaluation (2 treatment days)
- Xibrom™ achieved statistically significant reduction from baseline at all study visits

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*Data presented in following slides represent patients treated with Xibrom as their only anti-inflammatory (no steroid used)*

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*Data represent results from patients on Xibrom or placebo, only. No rescue medications.*
**Xibrom™ US Phase III Trials: Individual Mean Cell and Flare Scores by Visit**

- Xibrom statistical significance achieved on 1st treatment visit for both cell and flare reduction
- Statistical significance achieved through each treatment visit: Days 8 to 15

**Acular® 0.5% Pivotal Trial: Statistical Significance Achieved within 6 – 14 Day Measures**

In this specific study, use of NSAIDs pre-operatively was disallowed

- Reduction in Cells
- Reduction in Flare
- Patients Achieving Summed Cells & Flare Score of Zero
- Reduction in Ocular Pain

**Overall Pain Relief: Percentage of All Xibrom™ Subjects Pain Free**

- No patients in Xibrom group reported pain at day 14
- Subjects with 2 missing data points on day 1 were treated as treatment failures.
- Missing data were treated as LOCF

**Xibrom™: Summary Of Phase III Efficacy Results**

Statistical Significance Achieved in Every Time-Point Measure

- Use of NSAIDs pre-operatively was disallowed
- Statistical Significance Achieved within 6 – 14 Day Measures

**Xibrom™ US Phase III Trials: 2ndary End Point**

Time to Resolution of Ocular Pain

- Estimated median for Time to Resolution of Ocular Pain: Xibrom = 2.0 days ; Placebo = 5.0 days (p = 0.0001)

**Xibrom™ Post-Approval US Trials**

- Comfort vs. Acular LS
  - H.D. Perry, MD, T.Y. Chou, MD
- Physician Satisfaction
  - 589 Ophthalmologists/ 12,033 Patient Experiences
- CME Treatment Post-Cataract Surgery vs. Acular and Voltaren
  - D.S. Rho, MD, S.M. Soll, MD, B.J. Markovitz, MD
- Macular Edema Treatment Post-Glaucoma Surgery vs. Acular
  - A.M. Solish, MS, MD
**Xibrom™ Post-Approval Trials: Comfort**

A Comparison of Xibrom™ and Acular® LS in a Test of Comfort and Corneal Anesthesia

**Purpose:**
- Compare comfort of Xibrom and Acular LS
- 20 normal healthy volunteers

**Methods:**
- 20 subjects administered single drop of each test agent to their eyes in a random and masked fashion.
- Burning and stinging on a 0 – 4 scale.

**Results: Subjective Assessment of Comfort Upon Instillation**

<table>
<thead>
<tr>
<th>Level of Burning &amp; Stinging</th>
<th>Xibrom</th>
<th>Acular LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Physician Satisfaction – Xibrom First Experience (XFE) Trial**

- MDs placed a minimum of 10 patients on Xibrom
  - May through June, 2005
  - Jan through Mar, 2006
- MDs rated Xibrom performance:
  - Very Satisfied: “Exceeded My Expectations”
  - Satisfied: “Met All My Expectations”
  - Dissatisfied: “Met Some of My Expectations”
  - Very Dissatisfied: “Did Not Meet My Expectations”

- Robust MDs experiences captured:
  - 589 MDs reported to date
  - 12,033 patients experiences reported

**Xibrom™ Phase 4 Trials: Cystoid Macular Edema (CME)**

A Comparison of Bromfenac, Ketorolac, and Diclofenac for Treatment of Acute Pseudophakic Cystoid Macular Edema (Preliminary Data)

**Purpose:**
- Comparison of Xibrom, Acular, and Voltaren for treatment of acute CME post-cataract surgery

**Methods:**
- 64 post-cataract patients with acute CME randomized to one of three regimens: Xibrom BID, Acular QID, or Voltaren QID, in the affected eye
- Visual acuities measured; Snellen VA charts and ETDRS charts

**Results:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ETDRS Letters gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>15.0 ± 11.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>11.5 ± 7.5</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>11.6 ± 8.6</td>
</tr>
</tbody>
</table>

**P-values for ETDRS letters gained within treatment groups:**
- Bromfenac vs Diclofenac: p = 0.08
- Diclofenac vs Ketorolac: p = 0.26
- Ketorolac vs Diclofenac: p = 0.04

**P-values for ETDRS letters gained between treatment groups:**

**Xibrom™ Phase 4 Trials: Cystoid Macular Edema (CME)**

- Rho DS. ARVO 2006; A5211

**References:**
- Rho DS. ARVO 2006; A5211
**Xibrom™ Phase 4 Trials: Macular Edema Treatment Post-Glaucoma Surgery**

**A Prospective, Randomized Comparison of Bromfenac with Ketorolac for the Treatment of Patients with Reduced Visual Acuity Following Glaucoma Surgery**

*Alfred M. Solish, MS, MD*

**Purpose:**
- Comparison of Xibrom and Acular for treatment of macular edema post-glaucoma surgery

**Methods:**
- 20 post-glaucoma surgery patients with decreased corrected visual acuity (VA), whose vision had not improved with topical steroids, were randomized to either Xibrom BID or Acular QID
- Corrected visual acuities were compared following 4-6 weeks of treatment

<table>
<thead>
<tr>
<th></th>
<th>Bromfenac</th>
<th>Ketorolac</th>
<th>P (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial IOP (mmHg)</td>
<td>9.7±5.8</td>
<td>6.7±4.2</td>
<td>0.048</td>
</tr>
<tr>
<td>Follow-up IOP (mmHg)</td>
<td>11.8±8.2</td>
<td>8.3±6.3</td>
<td>0.093</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>46.3±23</td>
<td>34.7±21.7</td>
<td>0.071</td>
</tr>
<tr>
<td>Change in VA (lines corrected)</td>
<td>+1.5±2.6</td>
<td>+0.3±1.6</td>
<td>0.073</td>
</tr>
<tr>
<td>Patients gaining VA (&gt;2 lines)</td>
<td>6/16 (37.5%)</td>
<td>4/19 (21%)</td>
<td></td>
</tr>
<tr>
<td>Patients losing VA (≥1 line)</td>
<td>2/16 (12.5%)</td>
<td>5/19 (26.3%)</td>
<td></td>
</tr>
</tbody>
</table>

More patients had VA improvement with Xibrom than with Acular, though the difference was not statistically significant

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**Penetration & Potency Data**

Helps answer the question: *How and why is Xibrom BID?*

**Chemical Structures and Related Activities**

**Bromfenac**

**Amfenac**

Chemical structure of bromfenac is similar to amfenac, shown above:
- Substitution of the benzoyl ring has pronounced effects on *in-vivo* and *in-vitro* potency and absorption (B > 2x more potent than A in this study)\(^1\)
  - In general, compounds that contain a halogen, are more potent (I-~ Br- > Cl > F > H)\(^1\)


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**Octanol/Water (O/W) Partition Coefficients**

The octanol/water partition coefficient for bromfenac compared to other NSAIDs and Steroids at physiological pH 7.4\(^*\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>O/W Partition Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>2.23</td>
</tr>
<tr>
<td>Amfenac(^1)</td>
<td>1.23</td>
</tr>
<tr>
<td>Ketorolac(^2)</td>
<td>1.83</td>
</tr>
</tbody>
</table>

\(^1\) The higher the coefficient, the higher the penetration across membranes. 1.0 unit difference = 10 fold difference\(^1\)
Concentrations of Radioactivity in Ocular Tissues Following a Single Topical Ocular Dose of $^{14}$C-Bromfenac

1. Baklayan GA. ASCRS 2006;P227.

Detectable levels thru 24 hours and beyond for the above ocular tissues

Comparison of Ocular Concentrations of $^{14}$C- Bromfenac and $^{14}$C-Nepafenac

- Retina and choroid detectable through 24 hour time-point
- Retina not detectable at 6 hours
- Choroid not detectable at 12 hours

Concentrations of Radioactivity in Ocular Tissues Following a Single 0.09% Topical Ocular Dose of $^{14}$C-Bromfenac

1. McNamara TR. ARVO 2006;A5086.

Detectable levels thru 24 hours and beyond for the above ocular tissues

PK Profile of a Single 0.09% Topical Ocular Dose of Bromfenac in Subjects Undergoing Cataract Surgery

1. Ogawa T. ARVO 2006;A687.

IC50 value of bromfenac in human and rabbit COX-2 inhibitory activity

PK parameters of bromfenac in aqueous humor of human and rabbit
PK Profile of a Single 0.09% Topical Ocular Dose of Bromfenac in Subjects Undergoing Cataract Surgery

Estimation of duration for retaining the effective concentration of bromfenac after instillation over the IC50 value of COX-2

COX-2 Hypothesis

Relative Potency of NSAIDs In Vitro: IC50 vs COX-1 and COX-2 enzymes

Potency Measurement: IC50

Drugs concentration required to inhibit enzyme activity by 50%

The smaller the number, the more potent the molecule

Xibrom™ Safety

Extensive testing from Phase I – Phase III

6 years of ophthalmic use

Over 10.3 million ophthalmic uses

3,425 patients officially tracked by 703 institutions

A very safe drug:

No reported drug related serious systemic side effects

Xibrom™ US Phase III Trials: Common Treatment-Emergent Ocular Adverse Events (≥ 2% incidence rate)

Clinical studies demonstrated a minimal incidence of adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Xibrom™ (n = 356)</th>
<th>Placebo (n = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itch</td>
<td>25 (7.0%)</td>
<td>31 (18.1%)</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>15 (4.2%)</td>
<td>20 (11.7%)</td>
</tr>
<tr>
<td>Abnormal sensation in eye</td>
<td>23 (6.5%)</td>
<td>14 (8.2%)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>14 (3.9%)</td>
<td>5 (2.9%)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>9 (2.5%)</td>
<td>8 (4.7%)</td>
</tr>
<tr>
<td>Eye redness</td>
<td>8 (2.2%)</td>
<td>13 (7.3%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>7 (2.0%)</td>
<td>10 (5.7%)</td>
</tr>
</tbody>
</table>

Other Reported Adverse Events:

- ONLY 1.4% incidence of burning and stinging in Xibrom patients
- CME reported: Xibrom 1.4% - Placebo 4.7% (p = 0.05)

Note: Xibrom is not indicated for the treatment of CME nor Photophobia
Experience with Bromfenac Sodium Ophthalmic Solution in Japan (2000-2006)

- **10.3 million** uses & in over **7.8 million** patients in Japan
  - Zero drug related serious systemic events reported
  - Serious ocular adverse events
    - Reported in 0.0002% of patients (16)
- 14 corneal events reported in the Japanese post-marketing surveillance program involving 3,425 patients observed from May 2000 to January 2004 (0.41%).
- Dosing schedules, length of therapy, and indications may vary between Xibrom and bromfenac ophthalmic solution used in Japan
- Products in Japan and U.S. are identical

Well established “6 Year” safety profile

1. Data on file. ISTA Pharmaceuticals

Summary of Xibrom™

- **A Very Potent NSAID**
  - IC50 data for bromfenac & diclofenac & amfenac in similar models
- **Rapidly Treats Significant Inflammation**
  - Excellent penetration
- **BID dose**
  - Compliance & Convenience
- **Comfortable**
  - 1.4% burning/stinging
- **Safe**
  - 6 years experience & 10.3 million uses

Xibrom™ (Bronuck) Post Marketing Safety Report (Japan)
Filed with Minister of Health, Labour and Welfare 3/2005

- Marketed since 7/2000: There have been no drug related serious systemic adverse events reported with use of bromfenac sodium ophthalmic solution
- Xibrom, in the US, is indicated for BID dosing for 14 days of treatment

Xibrom™ US Phase III Trials: Grading Scale for Cells & Flare

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells (Count)</th>
<th>Grade</th>
<th>Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-5 (trace)</td>
<td>0</td>
<td>Complete Absence</td>
</tr>
<tr>
<td>1</td>
<td>6 - 15</td>
<td>1</td>
<td>Very Slight</td>
</tr>
<tr>
<td>2</td>
<td>16 - 25</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>26 - 50</td>
<td>3</td>
<td>Marked</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 50</td>
<td>4</td>
<td>Intense</td>
</tr>
</tbody>
</table>

Inclusion Criteria:
Patients were required to have a Summed Ocular Inflammation Score (cell score + flare score) ≥ 3 at 16 to 32 hours, **after surgery – PRIOR to Treatment**

Xibrom™: US Phase III Trials

Patients with EXISTING significant inflammation were treated with Xibrom, or placebo, BID

- Treatment started **AFTER** inflammation had developed
- Cells & flare graded each visit
- 1st treatment visit: 2 days of Xibrom treatment
Safety Issues have occurred with all ORAL NSAIDs

- Diclofenac (Voltaren®)
  - Gastrointestinal perforations, ulcerations, and bleeding
- Ketorolac (Toradol®)
  - Gastrointestinal perforations, ulcerations, and bleeding
  - Black box warning in U.S., withdrawn from market in France and Germany
  - 143 deaths from 1990-1993
- Bromfenac (Duract™)
  - Hepatotoxicity, acute hepatic failures, when used outside of labeled dosage
  - Manufacturer voluntarily withdrew from US market
  - 4 deaths in 1997-1998

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Xibrom™ US Phase III Trials: Liver Function Tests Show No Effect on Liver

<table>
<thead>
<tr>
<th>Liver Function Test</th>
<th>Xibrom™ (n = 340)</th>
<th>Placebo (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>3 (0.9%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Alanine transaminase (ALT)</td>
<td>4 (1.2%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>γ-glutamyl transpeptidase (GGT)</td>
<td>8 (2.3%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No significant differences between treatment groups
- No subjects with results = CTC grade 1

CTC = common toxicity criteria

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