MOBIC CLINICAL OVERVIEW
AND
WHAT’S UP WITH THE NSAIDS?????

Leo M. Rozmaryn, MD
November 2004
NSAID OVERVIEW

- 1 billion people world-wide have “arthritis”
- 30-50% are chronic NSAID users
- In U.S. 13 million use Rx.NSAIDS
- The same number use “over the counter” NSAIDS
NSAID RISKS

- 107,000 NSAID users hospitalized for GI
- 16,500 deaths due to GI bleeds (10-15%)
- Total cost $2 billion annually
Number of Deaths from Selected Causes
US population (1997)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>20,197</td>
</tr>
<tr>
<td>HIV</td>
<td>16,685</td>
</tr>
<tr>
<td>NSAIDs GI</td>
<td>16,500</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>10,503</td>
</tr>
<tr>
<td>Asthma</td>
<td>5,338</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>4,441</td>
</tr>
<tr>
<td>Hodgkin's Disease</td>
<td>1,437</td>
</tr>
</tbody>
</table>

Wolfe, Lichtenstein, and Singh, 1999 NEJM
Cyclo-oxygenase concepts

- Arachidonic acids (AA)- unsaturated fatty acid obtained from ingested animal fats
- Cyclo-oxygenase (COX) binds AA to form prostaglandins
- In 1991 a second “type” of COX was discovered
COX-1

- Constitutive enzyme: stable body concentration
- In many tissues and function varies depending on location
- Stable gene expression
  - Thromboxane production (TxA2)
  - Stomach mucus production
  - Kidney: water, Na retention
  - Platelet aggregation, adhesion ("stickiness")
  - Vasoconstriction
Cox-2

- Inducible by noxious (inflammation producing) stimulus
- Lives in endothelial blood vessel walls
- Variable gene expression
  - Prostacyclin production (PGI2)
  - Dilates blood vessels, permeability
  - Prevents platelet activation
  - Promotes extra-vascular phagocyte migration
Positive feedback mechanism

In response to local platelet aggregation by thromboxane, prostacyclin is produced in vessel walls to vasodilate and to curb TxA2 production.

Platelet aggregation doesn’t go unchecked
Cell membrane phospholipids

Phospholipase $A_2$

Arachidonic acid

Cyclooxygenase 1 and 2

Prostaglandin $H_2$

Thromboxane $A_2$

Prostaglandin $D_2$

Prostaglandin $E_2$

Prostaglandin $F_2$

Prostacyclin
Figure 3: The Current COX concept

- **Arachidonic Acid**
  - **COX-1** (Constitutive)
    - Inhibition undesirable
    - Homeostatic functions
      - Gastrointestinal tract
      - Renal tract
      - Platelet Function
      - Macrophage differentiation
  - **COX-2** (Induced)
    - Inhibition desirable
    - Inflammation
      - Cytokines IL-1, TNF
      - Growth factors
      - Glucocorticoids
      - Cytokines IL-4
Cox-1 vs. Cox-2 enzyme functions

- **Cox-2 enzyme**
  - inflammatory stimulus
  - inflammatory prostaglandins
    - contributes to:
      - pain
      - heat
      - swelling

- **Cox-1 enzyme**
  - dietary arachidonic acid
  - "housekeeping" substances
    - platelets (for blood clotting)
    - prostaglandin E₂ (for kidney function)
    - prostaglandin I₂ (for stomach protection)

- physiological stimulus
Platelets

Arachidonic acid

Aspirin blocks

COX-1

Platelet cells

Thromboxane

Blood Vessels

Arachidonic acid

COX-2 inhibitors block

Aspirin acetylates

COX-2

Endothelial cell

I5R-HETE

Neutrophil

ATL

Reduced clotting

Reduced inflammation
NSAID ACTION

- Block the receptor site for AA on the COX molecule so that it cannot convert AA into PGE, TxA1, PGI2
- Aspirin acetylates Cox-1 permanently so it has a longer duration of action
- Blockage is incomplete for COX-2 (big receptor site) so some PGI2 still made
- You need high ASA dose for NSAID effect (4000mg.) but just 75 mg for anti platelet effect = cardio-protective
Acetaminophen

- Has mild Cox-1 and Cox-2 inhibition effect
- Enough activity in the brain to relieve pain and fever
- ? Cox-3
Block COX-1

- Block production of Thromboxane
- Prevent platelet aggregation
- “Thin blood”
- Lose GI mucus “protective” effect
Block COX-2

- Diminish pain and inflammation
- Will allow Thromboxane synthesis to go unchecked by suppressing PGI2
- Vasoconstriction and runaway platelet aggregation and thrombus formation

- Science 4/19/02
Inhibiting COX –2 (PGE-2) in the kidney can cause Na+ and water retention causing hypertension.
Drug Regulation in Controversy: Vioxx
November 10, 2004

Sandra L. Kweder, M.D.
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
COX-2 Inhibitors

1990s: tremendous hope of reducing GI morbidity and mortality

1998 Vioxx NDA was large
- > 5000 pts
- Exposure up to 86 weeks, with 371 and 381 patients taking 12.5 and 25 mg/day for one year or longer; 272 patients took 50 mg for at least six months
- No CV signals in clinical trials, but reviewed carefully because of concern of pro-thrombotic effects *in vitro*
Vioxx 1999

January
- Vioxx GI Outcomes Research trial begins (VIGOR)

April - Arthritis Advisory Committee
- Efficacy and multiple safety components

May – Vioxx NDA approved
- Acute pain, dysmenorrhea, OA

November
- Colon polyp prevention study (APPROVe) submitted
# Coxib Study Designs

<table>
<thead>
<tr>
<th></th>
<th>CLASS(^1) (n=7968)</th>
<th>VIGOR(^2) (n=8076)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Celecoxib 400mg bid (4x OA dose, 2x max RA dose)</td>
<td>Rofecoxib 50mg qd (2x typical OA dose, 2x max chronic dose)</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>OA (72%), RA (28%)</td>
<td>RA</td>
</tr>
<tr>
<td><strong>Comparator(s)</strong></td>
<td>Ibuprofen 800mg tid, Diclofenac 75mg bid</td>
<td>Naproxen 500mg bid</td>
</tr>
<tr>
<td><strong>Low dose aspirin</strong></td>
<td>Yes (21%)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Median 9 months, Maximum 13 months</td>
<td>Median 9 months, Maximum 13 months</td>
</tr>
<tr>
<td><strong>1° endpoint</strong></td>
<td>Complicated ulcers</td>
<td>Clinical UGI events</td>
</tr>
<tr>
<td><strong>2° endpoint</strong></td>
<td>Symptomatic ulcers</td>
<td>Complicated UGI events</td>
</tr>
</tbody>
</table>

\(^1\) Celecoxib Long-term Arthritis Safety Study  
\(^2\) Vioxx Gastrointestinal Outcomes Research
VIGOR: Kaplan-Meier cumulative rate of complicated PUBs (per 100 patient-years)$^{2*\dagger}$

- Rofecoxib 50 mg/day: 0.52
- Naproxen 500 mg BID: 1.22
Vioxx 2000

March – Preliminary results of VIGOR submitted to IND
- Analyses of serious CV events in all NDA studies, placebo controlled Alzheimer studies and ADVANTAGE, which was almost complete
- Letters to all investigators with information
- Informed consent documents modified

Multiple public venues for data
Vioxx 2000 (continued)

- **June**
  - APPROVe protocol changed to allow use of low dose aspirin

- **June – VIGOR to FDA as NDA supplement**
  - Decrease in risk of gastro-duodenal perforations, ulcers and bleeds compared to naproxen
  - Increase in CV thrombotic events, mostly MI 0.5% V vs. 0.1% not used

- **November – NEJM publication of VIGOR**
February
- Arthritis Advisory Committee reviews VIGOR
- Risk/Benefit review – still positive
- Recommend labeling & additional studies of CV risk

February**
- NDA for Rheumatoid Arthritis submitted
- N=1100 taking 25 or 50 mg vs naproxen for 3-12 months

Fall
- APPROVe completes enrollment
- Labeling discussions with Merck ongoing
Vioxx 2001 (continued)

- All Vioxx protocols reviewed
  - Alzheimer's, polyps, prostate cancer
  - Focus on CV endpoint definition & adjudication
- Review of data sources for more definitive answer
  - NDA supplement for RA
  - Interim analyses of other clinical trials
- FDA sought large database to conduct retrospective data review
  - Contract with Kaiser
Vioxx 2002

- Label discussions between FDA and Merck

- Ongoing data review by FDA
  - Mixed picture of CV risk
  - Merck submits more data from ongoing Alzheimer’s Disease trials
    - 2800 patients on Vioxx 25 mg vs placebo
    - No excess of CV events

- April
  - Label for RA, GI safety benefit and CV risk approved
  - CV risk in “Precautions” and other sections
  - 50 mg dose should not be used for more than 5 days
Vioxx 2003-2004

- 2003
  - Continued focus on ongoing trials and data collection and assessment for CV safety

- August 2004
  - FDA Kaiser cohort analysis neared completion
  - Abstract presented at ISPE
    - Shows risk of 50 mg dose (confirms VIGOR)
    - Risk for 25 mg dose similar to other NSAIDS

- September 2004
  - APPROVe 36 month study results reviewed by DSMB
  - Merck decision to withdraw Vioxx
What Did APPROVe Show?

- Vioxx 25 mg per day significantly increases risk of serious CV events (MI and stroke) compared to placebo.
- Risk appears after patients are taking drug for 18 months.
  - Definitive confirmation of risk not evident until 36 month assessment.
VIGOR: Kaplan-Meier cumulative rate of CV thrombotic adverse events (per 100 patient-years)

- Rofecoxib 50 mg/day: 1.81
- Naproxen 500 mg BID: 0.6
Number of subjects in studies included in meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Valdecoxib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott (initial CABG study)</td>
<td>311</td>
<td>151</td>
</tr>
<tr>
<td>2nd CABG</td>
<td>1088</td>
<td>548</td>
</tr>
<tr>
<td>White (placebo-controlled studies only)</td>
<td>4531</td>
<td>1142</td>
</tr>
</tbody>
</table>

Valdecoxib (Bextra) meta-analysis signals significant cardiovascular risk
[Rheumawire > News; Nov 10, 2004]
### Number of cardiovascular events (MI and stroke)

<table>
<thead>
<tr>
<th>Study</th>
<th>Valdecoxib</th>
<th>Placebo</th>
<th>RR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Ott</td>
<td>14</td>
<td>2</td>
<td>3.51</td>
<td>0.79-16</td>
</tr>
<tr>
<td>2nd CABG</td>
<td>17</td>
<td>3</td>
<td>2.88</td>
<td>0.84-10</td>
</tr>
<tr>
<td>White</td>
<td>14</td>
<td>2</td>
<td>1.77</td>
<td>0.40-7.8</td>
</tr>
<tr>
<td>Meta-analysis, p=0.11</td>
<td></td>
<td></td>
<td>2.19</td>
<td>1.19-4.03</td>
</tr>
</tbody>
</table>

Valdecoxib (Bextra) meta-analysis signals significant cardiovascular risk

[Rheumawire > News; Nov 10, 2004]
Do Cox-2 Selective Agents Have a Different CV Risk Profile?

- No definitive evidence – except Vioxx
- Agents differ in degree of selectivity
- Dose response may be an important factor
- Traditional NSAIDs may differ in CV toxicity profiles
- Mechanism for the risk remains unclear
  - platelet effect?
  - blood pressure?
  - Other?
Difficulties in Evaluation

- Placebo controlled data most interpretable because CV effects of comparators not established
  - Issue of naproxen control loomed over VIGOR
  - Other NSAID controls would have similar concerns
- VIGOR suggested risk seems to be highest after months on treatment
  - Hard to do long term placebo controlled trials in arthritis
  - Trials in high risk groups for long periods are of concern
  - High CV risk groups take ASA, which might have mitigated any adverse risk with Vioxx
What About Other COX-2s?
Celecoxib (Celebrex)

- Approved in 1998
  - No CV risk in NDA

- Development program
  - Large scale placebo-controlled trials for prevention of colon polyps/cancer (n=3600) and Alzheimer’s disease
  - Independent DSMBs for these studies with special emphasis on cardiovascular events. Both DSMB’s get monthly data updates; have issued statements to investigators that they are aware of rofecoxib W/D and have determined there is no indication for stopping these trials
  - Meet again in late fall
Valdecoxib (Bextra)

- NDA database of 8,000
  - No CV signal in oral studies at doses in range and above those approved
  - No CV signal in IV studies in post operative pain
  - Excess CV events and death in single IV study in post-CABG patients
- IV and follow-on p.o. in post-op studies were 2-4X that in oral only studies
Valdecoxl (Bextra)
10/18/04

- Stevens-Johnson syndrome
- Exfoliative dermatitis
- Toxic epidermal necrolysis
- High rate with Bextra than any other NSAID
- Within first two weeks of treatment
- Very rare <1%
Bextra controversy

- Fitzgerald meta-analysis 2000 CABG patients
- 2 placebo controlled trials of Bextra
- 7500 in all, varying the NSAID for post op pain relief
- Twice the incidence of MI or CVA with Bextra than any other NSAID
Study design

- CABG patients were given IV Paracoxib post-op followed by Bextra po 40-80 mg
- Close exam of the MI’s showed that most occurred intra-op before the drug was given.
- The fun is just starting!
FDA Next Steps

Arthritis Advisory Committee in early 2005
- Share all available data on Vioxx and other drugs
- Seek advice on additional steps and studies needed

Other COX-2s
- Accumulating data re: celecoxib via placebo controlled trials
- Explore ways of further evaluation of valdecoxib
- Scrutiny of new agents (some approved in Europe)
FDA Safety Initiative 2004

- Search for Director, Office of Drug Safety
- Institute of Medicine Study
  - Assess full spectrum of drug safety in the US
  - To include operations between Office of New Drugs and Office of Drug Safety
- New procedure for review of differing professional opinions
  - When usual processes are not satisfactory to parties
- Focused effort to bring safety matters to public Advisory Committee meetings for review
Summary

- Vioxx experience complex from scientific and regulatory standpoint
  - Data were mixed from very early on
  - Definitive trials in arthritis extremely challenging
  - Difficulty in requiring 3 year placebo controlled safety studies prior to approval
  - Placebo controlled data offered best hope for definitive answers

- The experience will be applied to review additional COX-2 inhibitors over next few months
  - Public discussion essential – Advisory Committee
Learning from experience is a part of public accountability

- Role for external scrutiny (IOM), particularly of broader picture of our ability to be effective in identifying and following up on safety issues
Well, what about Mobic?
Meloxicam Worldwide Experience: December 2000

- Approved in >100 countries worldwide
- Postmarketing data analyzed on 30,000 patients
- 160 clinical trials with 45,000 patients
- 45 million patients treated

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.
Meloxicam Pharmacokinetics

- **Absorption**
  - Peak plasma concentrations ($C_{\text{max}}$) at 5–6 hours
  - Steady state concentrations within 3–5 days
  - Half-life = 20 hours (true once-daily dosing)
  - Can be taken without regard to meals

- **Distribution**
  - Protein binding >99.5%
  - Synovial fluid concentration = 40%–50% of plasma concentrations

- **Excretion**
  - Eliminated by hepatic metabolism (no active metabolites)
  - Equal excretion via urinary and fecal routes

# Meloxicam Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>No</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No*</td>
</tr>
<tr>
<td>Furosemide</td>
<td>No</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>No</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No</td>
</tr>
<tr>
<td>Lithium</td>
<td>Yes†</td>
</tr>
</tbody>
</table>

* No change in INR with concomitant meloxicam therapy  
†21% increase in lithium AUC

-Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.
COX1- COX2 Balance

- In vitro inhibition of COX 2 is 3x that of COX-1
- Diminished monocyte (COX-2) activity by 50-70%
- Diminished platelet (COX-1) activity by 25-35%
Efficacy
Efficacy Overview

- US OA Trial
- US RA Trial
- IMPROVE
- Ankylosing spondylitis
Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial

Trial Design

- Double-blind, parallel group, randomized multi-center study (774 patients)
- Patient aged 62.9 +/- 10.3 years
- Diagnosis of OA of hip or knee and a flare
- Treated with meloxicam (3.75mg, 7.5 mg, 15 mg/d), diclofenac (100mg [50mg twice daily]), or placebo for 12 weeks
Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial

Incidence of gastrointestinal adverse events estimated using the Kaplan-Meier algorithm.

Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial

**WOMAC Total Score: Pain, Function, Stiffness**

- Placebo
- Meloxicam, 3.75 mg/d
- Meloxicam, 7.5 mg/d
- Meloxicam, 15 mg/d
- Diclofenac, 50 mg BID

- *P < .001 (Significantly Different From 0)
- †P < .05 Compared With Placebo
- ‡P < .001 Compared With Placebo

Reduction in pain over the previous 2 days in RA for meloxicam 15 mg and piroxicam 20 mg

Huskisson et al. Scand J Rheumatol 1994 (suppl. 98): 115
Improvement from baseline in total WOMAC score (%)

- MOBIC® (n=662) 22%
- Celebrex® (Celecoxib) (n=78) 24%
- Vioxx® (rofecoxib) (n=151) 17%
- Diclofenac (n=66) 10%
- Naproxen (n=70) 18%
- Nabumetone (n=44) 5%
- Ibuprofen (n=18) 1%
Prescription NSAIDs and COX-2s (n=643)

MOBIC (n=662)

57%

14%

22%

WOMAC Improvement From Baseline

IMPROVE Trial
IMPROVE Trial
Patient Success

Patient success rate (%)

MOBIC®
(n=662)
Other NSAIDs
N=647)
Celebrex®
(n=79)
Vioxx®
(n=151)
Diclofenac
(n=66)
Naproxen
(n=71)
Nabumetone
(n=46)
Ibuprofen
(n=18)

67%
45%
62%
54%
42%
41%
28%
39%
Absolute change in disease activity over 1 year of treatment in patients with AS

Change in disease activity (mm VAS)

* p<0.05 vs meloxicam and piroxicam

Placebo (n=121)
Meloxicam 22.5 mg (n=120)
Meloxicam 15 mg (n=120)
Piroxicam 20 mg (n=108)

Dougados et al. Rheumatology 1999; 38:235-244
Efficacy Summary

Meloxicam 7.5-mg dose demonstrates efficacy clinically comparable to diclofenac 100 mg SR and piroxicam 20 mg.

Meloxicam 7.5-mg and 15-mg doses demonstrate:

- Efficacy significantly superior to placebo for all efficacy measures
- Significantly fewer withdrawals than placebo due to lack of efficacy

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission
GI Safety and Tolerability
GI Safety and Tolerability Overview

- US OA Trial
- MELISSA/SELECT
- CLASS/VIGOR
- GI Adverse Event Meta-analysis
Total GI AEs and Withdrawals Due to GI AEs: US OA Trial

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission
MELISSA and SELECT

**Trial Design**

**MELISSA:**
- International prospective trial (n=9323)
- Double-blind, double-dummy, randomized trial
- Purpose to investigate tolerability of meloxicam compared to diclofenac.
- Conducted over 28 days in patients with symptomatic OA
- Compared meloxicam 7.5mg vs. diclofenac 100mg

**SELECT:**
- Large-scale prospective international trial (n=8656).
- Double-blind, double-dummy, randomized parallel group trial
- Meloxicam 7.5mg vs. piroxicam 20mg
Patient’s and Investigator’s Global Efficacy Assessment: MELISSA and SELECT

Patient’s Assessment

Most effective

Mean Value

MELISSA

SELECT

(n=4,635) (n=4,688)
(n=4,320) (n=4,336)

(n=4,635) (n=4,688)
(n=4,320) (n=4,336)

Meloxicam 7.5 mg

Diclofenac 100 mg SR

Piroxicam 20 mg

Least effective
Total GI AEs and Withdrawals
Due to GI AEs: MELISSA and SELECT

MELISSA

- Meloxicam 7.5 mg (n=4,635): 13.0%
- Diclofenac 100 mg SR (n=4,688): 19.0%

SELECT

- Meloxicam 7.5 mg (n=4,320): 10.3%
- Piroxicam 20 mg (n=4,336): 15.4%

Due to total GI AEs:

- * P<0.001 vs comparator drug
- † P<0.05 vs comparator drug

Incidence of most common GI AEs was significantly lower with meloxicam 7.5 mg than with diclofenac 100 mg SR and piroxicam 20 mg

- Dyspepsia ($P < 0.001$)
- Nausea/vomiting ($P < 0.05$)
- Abdominal pain ($P < 0.001$)
- Diarrhea ($P < 0.001$)*

* MELISSA (diclofenac) only

Meloxicam Serious GI Event Meta-Analysis Objective

- Determine the risk of clinically serious GI Events (Perforation, Obstruction, or Bleeds) in patients receiving meloxicam.
GI Safety and Tolerability Meta-Analysis Protocol

Identification of 10 published trials (>20,000 patients) meeting the following criteria

- Comparison of meloxicam with another NSAID
- Adult patient population
- Randomized trial with parallel design or crossover with washout
- Evaluation of GI adverse events

Test for homogeneity

- $P > 0.05$ indicates trial homogeneity

Trials Included in Meta-analysis

- 35 clinical trials (27,309 patients)
  - 21 Controlled
    - 7 Diclofenac (6 OA, 1 RA)
    - 2 Naproxen (RA)
    - 10 Piroxicam (6 OA, 2 RA, 1 AS, 1 other)
    - 2 Placebo (1 OA, 1 RA)
  - 11 Uncontrolled
  - 3 Long Term extension
Meloxicam Serious GI Event Meta-Analysis

- Total Number of patients: 27,309
- Cases reviewed: 448
- Confirmed GI Events: 54
  - UGI source: 37
  - Source unknown: 10
  - Not enough data: 7
Incidence of Serious GI Adverse Events
Meta-analysis Study: Limitations

- Pooling of data
  - similar results in active-controlled, placebo-controlled and uncontrolled studies, different indications

- Post-hoc analysis of prospective data
  - ascertainment bias

- Limited duration of exposure (7.5 mg)
Meta-analysis Study

Strengths

- Patients not screened or selected
  - did not exclude patients with
    - a history of ulcer disease
    - asymptomatic endoscopic detectable ulcers
    - elderly

- Generalizability
Meloxicam Meta-Analysis Summary

In a meta-analysis of 10 published trials, meloxicam resulted in a lower risk for GI adverse events compared with diclofenac, piroxicam, and naproxen.

<table>
<thead>
<tr>
<th>GI Event</th>
<th>Approximate risk reduction with Meloxicam</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI AEs</td>
<td>36%</td>
</tr>
<tr>
<td>Withdrawals (GI AEs)</td>
<td>41%</td>
</tr>
<tr>
<td>PUBs</td>
<td>48%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>27%</td>
</tr>
</tbody>
</table>

Endoscopy data

- 28 day study
- Mobic 7.5 MG <= 15 mg or Piroxicam 20mg with regard to ulcerations and gastric or duodenal irritation
Meloxicam Safety and Tolerability Summary

- Low incidence of GI AEs
- GI tolerability is statistically superior to that of other NSAIDs (diclofenac and piroxicam)
- GI tolerability is comparable to placebo

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./
Yocum et al. Pending MS submission.
Cardiovascular, Renal, and Hepatic Safety
Cardiovascular, Renal, and Hepatic Safety Overview

- Myocardial Infarctions
- Blood pressure
- Thromboembolic events
- Peripheral edema
- Hepatic safety
Myocardial Infarctions

Melox 7.5 0.54%
Melox 15 mg 0.90%
Melox 22.5 mg 0.00%
Melox 30 mg 0.00%
Diclo 0.95%
Pirox 0.50%
Naprox 0.00%
Placebo 1.77%

per 100 Pt-years (%)

Total Treated 10,158 2,960 910 1,043 5,464 5,371 243 763

per 100 years POB DATABASE
### Effect on Blood Pressure

**Change From Baseline by Dose**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Systolic BP (mean change from baseline)</th>
<th>Diastolic BP (mean change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam 7.5</td>
<td>-1.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>Meloxicam 15</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Meloxicam 22.5</td>
<td>-0.1</td>
<td>-1.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.4</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

Source: OA NDA, ISS, TABLE 8.8.9.1: 1 Vital Signs Summary for Controlled Phase 2/3 Trials by Treatment Group (Integrated Safety Database)

1. A patient must have had a baseline and at least one post-baseline vital sign measurement to be included in this table.
Thromboembolic Events

Melox 7.5 mg: 1.1%
Melox 15 mg: 1.4%
Melox 22.5 mg: 0.3%
Melox 30 mg: 0.0%
Diclofenac: 2.5%
Piroxicam: 0.8%
Naproxen: 0.0%
Placebo: 2.7%

Total Treated: 10,158

POB DATABASE
## Peripheral Edema

<table>
<thead>
<tr>
<th>Trial</th>
<th>Meloxicam (n)</th>
<th>Peripheral Edema</th>
<th>Weight Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELISSA Trial</strong></td>
<td>Meloxicam (n = 4,635)</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (n = 4,688)</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>SELECT Trial</strong></td>
<td>Meloxicam (n = 4,320)</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Piroxicam (n = 4,336)</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>U.S. OA Trial</strong></td>
<td>Placebo (n = 157)</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Meloxicam (n = 464)</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (n = 153)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission
## Selected Cardiorenal Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Meloxicam</th>
<th>NSAIDs</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat patients (N)</td>
<td>15,071</td>
<td>11,078</td>
<td>736</td>
</tr>
<tr>
<td>Patient Years</td>
<td>3129</td>
<td>1202</td>
<td>113</td>
</tr>
<tr>
<td>Events (N, per 100 Pt yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>18 (0.58)</td>
<td>8 (0.67)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>15 (0.48)</td>
<td>7 (0.58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Edema, Peripheral</td>
<td>98 (3.13)</td>
<td>79 (6.57)</td>
<td>1 (0.88)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (2.62)</td>
<td>32 (2.66)</td>
<td>5 (4.42)</td>
</tr>
<tr>
<td>Hypertension, Aggravated</td>
<td>25 (0.8)</td>
<td>15 (1.25)</td>
<td>2 (1.77)</td>
</tr>
</tbody>
</table>

Singh, 2001

POB DATABASE
Risk of Serious Upper Gastrointestinal and Cardiovascular Thromboembolic Complications with Meloxicam: The POB Analysis
POB Data Analysis

- Pooled analysis of 28 clinical trials evaluated GI and thromboembolic safety profile of meloxicam
  - Evaluated risk estimates of thromboembolic and serious upper GI complications
  - Compared meloxicam to the traditional NSAIDs diclofenac, naproxen, and piroxicam

1. Mobic® (meloxicam) Prescribing Information, Ridgefield, CT.
Study Definitions

- **Serious GI complications**
  - Upper GI bleeding
  - Gastric outlet obstruction
  - Duodenal or gastric perforation

- **Thromboembolic events**
  - Coronary thrombosis
  - Cerebral infarction
  - Myocardial infarction
  - Transient ischemic attack
  - Stroke

Study Design

Trial Criteria
- Oral meloxicam therapy (7.5 mg and 15 mg)
- 21-day treatment minimum
- Sample size ≥20
- North America or Western Europe
- Study completed by April 1, 1999

Study Sample
- 28 Trials
- N=24,196

Treatment Groups
- Meloxicam 7.5 mg/15 mg (n=13,118)
- Diclofenac 100 mg/d/150 mg/d (n=5464)
- Naproxen 500 mg BID (n=243)
- Piroxicam 20 mg (n=5371)

## Risk Estimates

<table>
<thead>
<tr>
<th>Treatment (dose)</th>
<th>Interval (days)</th>
<th>Number of Patients Entering Interval</th>
<th>Serious GI Events</th>
<th>Thromboembolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-60</td>
<td>10,158</td>
<td>3 (0.03)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Meloxicam (7.5 mg/d)</td>
<td>&gt;60</td>
<td>551</td>
<td>0 (0.03)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Meloxicam (15 mg/d)</td>
<td>0-60</td>
<td>2960</td>
<td>5 (0.2)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>1684</td>
<td>4 (0.6)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Diclofenac (100-150 mg/d)*</td>
<td>0-60</td>
<td>5464</td>
<td>7 (0.1)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>493</td>
<td>2 (1.3)</td>
<td>0 (0.8)</td>
</tr>
<tr>
<td>Piroxicam (20 mg/d)</td>
<td>0-60</td>
<td>5371</td>
<td>15 (0.9)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>532</td>
<td>1 (1.1)</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>Naproxen (1000 mg/d)</td>
<td>0-60</td>
<td>243</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>166</td>
<td>0 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes 5283 patients treated with a 100-mg/d dose and 181 patients treated with a 150-mg/d dose.

<table>
<thead>
<tr>
<th>Treatment Compared</th>
<th>GI Complications</th>
<th>Thromboembolic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam 7.5 mg vs meloxicam 15 mg</td>
<td>0.06</td>
<td>0.8</td>
</tr>
<tr>
<td>Meloxicam 7.5 mg vs diclofenac</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Meloxicam 7.5 mg vs piroxicam</td>
<td>&lt;0.001</td>
<td>0.8</td>
</tr>
<tr>
<td>Meloxicam 7.5 mg vs naproxen</td>
<td>0.003</td>
<td>0.5</td>
</tr>
<tr>
<td>Meloxicam 15 mg vs diclofenac</td>
<td>0.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Meloxicam 15 mg vs piroxicam</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Meloxicam 15 mg vs naproxen</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Diclofenac vs piroxicam</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Diclofenac vs naproxen</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Piroxicam vs naproxen</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*By log-rank test.

Probability of Thromboembolic Complications

Probability of GI Complications

Study Limitations

- Majority of patients treated for <2 months
  - Long-term risk estimates are unreliable
- Absence of protocol-defined guidelines
- Randomization was not preserved with pooled analysis
- Accurate comparison would require head-to-head clinical trials

POB Data Analysis
Conclusions

- Data analysis suggests that in the first 60 days, the risk of serious upper GI complications is significantly lower in patients taking meloxicam 7.5 mg/d compared with those taking diclofenac, naproxen, or piroxicam.
- Risk of thromboembolic events was similar in all treatment groups evaluated.
- Meloxicam has a favorable thromboembolic and GI safety profile for up to 2 months of treatment.
Meloxicam Hepatic Safety

- No dosage adjustment required for patients with mild to moderate (Pugh grade 1 or 2) hepatic impairment

- Patients with severe hepatic impairment have not been studied; therefore, use of meloxicam is not recommended

- Favorable hepatic and renal safety profile

Meloxicam Cardio-Renal Safety

- Low risk of GI event at 7.5mg or 15mg
- No increased incidence of, or apparent association of:
  - MIs
  - Increase HTN
  - Peripheral Edema
  - Thromboembolic events
  - Strokes
  - Cardiorenal effects
  - CHF or AMI compared to non-selective NSAIDs

Meloxicam Platelet Aggregation and Bleed Time
Meloxicam

Bleeding Time at Steady State
Change from baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change from Baseline</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Melox 7.5</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Melox 15</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>Melox 30</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>* 1.6</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs placebo

Data on file, Study 107.236
Day 8, 6 Hours Post dose, Values are the means, not for the SE
Meloxicam
Platelet Aggregation at Steady State

*P < 0.05 vs placebo
1Data on file, Study 107.236
Day 8, 6 Hours Post dose to arachidonic acid, Values are the means, not for the SE
Meloxicam at higher than recommended doses had no effect on arachidonic acid-induced platelet aggregation and bleeding time.
IMPROVE Trial
Impact of Meloxicam on Prescription Regimens in Osteoarthritis Vs Everyday Care
IMPROVE Trial: Objective

To determine:

the percent of successes or failures of meloxicam vs prescription NSAIDs in patients with OA in MCO’s

Success:

- Satisfied with initial NSAID
- Did not switch to another NSAID
- Completed the study
IMPROVE Trial Study Design

• U.S., multicenter, blinded-randomized, open-label, parallel-group (N~1,200, ~ 600/arm)

• Patients aged >18 years

• Diagnosis of OA of the hip, knee, hand, or spine

• Willing to change NSAID therapy or

• Requiring
  ● initiation of an NSAID or
  ● change to a different NSAID

• Randomized to either meloxicam or any other prescription NSAID
<table>
<thead>
<tr>
<th></th>
<th>Meloxicam</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rand &amp; Treated (N)</td>
<td>662</td>
<td>647</td>
</tr>
<tr>
<td>Completed</td>
<td>91%</td>
<td>88.6%</td>
</tr>
<tr>
<td>Withdrew from study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>2.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Administrative</td>
<td>4.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>LOE</td>
<td>0.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Other</td>
<td>1.2%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**IMPROVE Trial: Patient Disposition**

ITT patient = randomized + took at least 1 dose of medication + at least one post-dose efficacy evaluation
## IMPROVE Trial

### Trial Demographics

<table>
<thead>
<tr>
<th></th>
<th>Meloxicam (N=662)</th>
<th>Usual Care (N=647)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>66%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40 yrs</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>41-50 yrs</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>51-60 yrs</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>61-70 yrs</td>
<td>31%</td>
<td>30%</td>
</tr>
<tr>
<td>71-80 yrs</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>&gt;80 yrs</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Mean Duration of OA</strong></td>
<td>9.5</td>
<td>9.7</td>
</tr>
</tbody>
</table>
## IMPROVE Trial
### POB and Ulcer History

<table>
<thead>
<tr>
<th>History</th>
<th>Meloxicam (N=662)</th>
<th>Usual Care (N=647)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Obstruction</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ulcer</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>NSAID</td>
<td>N</td>
<td>% of Total UC</td>
</tr>
<tr>
<td>----------------</td>
<td>------</td>
<td>---------------</td>
</tr>
<tr>
<td>VIOXX</td>
<td>151</td>
<td>23%</td>
</tr>
<tr>
<td>CELEBREX</td>
<td>79</td>
<td>12%</td>
</tr>
<tr>
<td>NAPROXEN</td>
<td>71</td>
<td>11%</td>
</tr>
<tr>
<td>DICLOFENAC</td>
<td>66</td>
<td>10%</td>
</tr>
<tr>
<td>PIROXICAM</td>
<td>58</td>
<td>9%</td>
</tr>
<tr>
<td>NABUMETONE</td>
<td>46</td>
<td>7%</td>
</tr>
<tr>
<td>ETODOLAC</td>
<td>38</td>
<td>6%</td>
</tr>
<tr>
<td>SULINDAC</td>
<td>35</td>
<td>5%</td>
</tr>
<tr>
<td>OXAPROZIN</td>
<td>34</td>
<td>5%</td>
</tr>
<tr>
<td>IBUPROFEN</td>
<td>18</td>
<td>3%</td>
</tr>
<tr>
<td>ARTHROTEC</td>
<td>13</td>
<td>2%</td>
</tr>
</tbody>
</table>
**IMPROVE Trial**  
*Non NSAID & Non Pharmacologic Tx*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Prior Use</th>
<th></th>
<th>During Study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melox %</td>
<td>UC %</td>
<td>Melox %</td>
<td>UC %</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>23</td>
<td>25</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Top/Inj Steroid</td>
<td>19</td>
<td>20</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Non Narc. Analgesic</td>
<td>14</td>
<td>15</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Non-Pharm Tx</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Glu/Chon Combo</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Narcotic Analgesic</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Acet with Codeine</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Local Anesthetic</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Study Conducted: 10/98-5/00
**IMPORVE Trial Successes**

- **Meloxicam**
  - Success: Completed the study and never switched, or completed study but no longer needed an NSAID during the trial for Tx of their OA
  - N=662
  - 67% (p < 0.0005 vs usual care)

- **Usual Care**
  - N=647
  - 45%
COX-1 Sparing Effects of NSAIDs
The Range of COX Selectivities

log [IC₅₀ ratio (WHMA COX-2 / COX-1)]

-3
-2
-1
0
1
2
3

all classical NSAIDs

no classical NSAIDs

ketorolac
ketoprofen
flurbiprofen
suprofen
ampyrone
fenoprofen
indomethacin
naproxen
tolmetin
ibuprofen
naprofen
aspirin
tolmetin
flurbiprofen
flurbiprofen
ketorolac

< 5-fold COX-2 selective

> 5-fold COX-2 selective

diclofenac
diflunisal
meclofenamate
tomoxiprol
piroxicam
sodium salicylate
niflumic acid
zomepirac
fenoprofen
ampyrone
ibuprofen
naprofen
aspirin
tolmetin
flurbiprofen
ketorolac

< 5-fold COX-2 selective

> 5-fold COX-2 selective

rofecoxib
etodolac
meloxicam
celecoxib
nimesulide
Hence Meloxicam is Cox-2 selective and not specific
“emerging data from animal, experimental, and clinical data suggest that COX –2 is atherogenic and thrombogenic and selective COX-2 inhibition may be cardio-protective”

Hence the “BALANCE” concept
Mobic® (meloxicam) tablets Safety Information

- The starting and maintenance dose for Mobic is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.
- Mobic is contraindicated in patients with known hypersensitivity to meloxicam. It should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Higher doses of Mobic (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore, the daily dose of Mobic should not exceed 15 mg.
- The most common GI side effects (≥3%) observed during clinical trials associated with use of Mobic are diarrhea, dyspepsia and nausea, although these effects occurred in less than 5% of patients.

1. Mobic® (meloxicam) Prescribing Information, Ridgefield, CT.
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