Update on Meloxicam (Mobicox®) & COX-2 Selectivity

**COX-2 Selectivity/Specificity**
- There is a lot of discussion regarding the relative COX-2 selectivity of meloxicam compared to celecoxib (Celebrex®) and rofecoxib (Vioxx®). A December 2000 RxFiles Q&A Summary regarding meloxicam stated that it had “relatively selective but not specific COX-2 inhibition” as discussed in a variety of literature.
- Boehringer Ingelheim (Canada) Ltd. (BICL) has been detailing meloxicam as an agent with COX-2 selectivity comparable to celecoxib based on data from BICL sponsored work of Warner et al.
- This research measured NSAID inhibition of COX-1 when COX-2 enzyme activity is inhibited by 80%. It found that both meloxicam and celecoxib were 5-50 fold selective for COX-2, with rofecoxib being >50 fold COX-2 selective.
- The interpretation of studies measuring relative COX-2 to COX-1 selectivity is subject to much debate due to differences in the various assays used. As with rofecoxib and celecoxib, meloxicam does not appear to affect platelet aggregation, a trait that supports high COX-2 selectivity.
- There is a lot of discussion regarding the relative COX-2 specificity which has been used for both celecoxib and rofecoxib. According to a recent memorandum, the Pharmaceutical Advertising Advisory Board (PAAB) has stated that “no product has received approval for use of the term ‘COX-2 specific’ in advertising because it is not in the product monograph of any of the three drugs” (Mobicox®, Vioxx®, and Celebrex®). A look at current evidence regarding actual safety data (e.g. risk of complicated GI ulcers) will be more relevant to this discussion.

**GI Tolerance and Safety**
- Unfortunately no head-to-head clinical data is available to compare rofecoxib or celecoxib to meloxicam.
- Two large-scale, short-term 28day trials have assessed the GI tolerability of meloxicam (see Table).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>NSAID</th>
<th>COX-2 IC50</th>
<th>COX-1 IC50</th>
<th>GI-ADRs</th>
<th>Ulcers</th>
<th>Major GI Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELISSA</strong></td>
<td>Meloxicam 7.5mg PO BID</td>
<td>Naproxen 375mg PO BID</td>
<td>~2.14</td>
<td>~29.7</td>
<td>1.98%</td>
<td>1.57%</td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>SELECT</strong></td>
<td>Meloxicam 20mg PO</td>
<td>Naproxen 375mg PO BID</td>
<td>~12.5</td>
<td>~29.7</td>
<td>0.48%</td>
<td>0.86%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>CLASS</strong></td>
<td>Rofecoxib 12.5mg PO BID</td>
<td>Naproxen 375mg PO BID</td>
<td>~12.5</td>
<td>~29.7</td>
<td>0.76%</td>
<td>1.57%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>VIGOR</strong></td>
<td>Rofecoxib 12.5mg PO BID</td>
<td>Naproxen 375mg PO BID</td>
<td>~12.5</td>
<td>~29.7</td>
<td>0.48%</td>
<td>0.86%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

- The fight over the COX-2 market share has resulted in this data must be cautiously interpreted due to the inherent limitations of the meta-analysis, such as variability of trial outcomes, and the low dosage of meloxicam used in most trials.
- Meloxicam appears to have better GI tolerance than non-selective NSAIDs. To what extent ulcers and complicated ulcers are also reduced remains to be established.
- Major trials evaluating the safety of the other COX-2 selective drugs, celecoxib (Celebrex®) and rofecoxib (Vioxx®) have been published. These trials differ from the large-scale meloxicam trials as dosages were 2-4X higher than usually recommended and trial length was longer.
- The CLASS study compared celecoxib to naproxen and found significant reductions in complicated ulcers in rofecoxib patients. As opposed to the CLASS trial, ASA patients were excluded from the study and a small increase in risk of acute MI was seen.
- These trial results pose many more questions that will require further study (& more updates).

Approximate cost per 30 day prescription in SK (includes allowable markup and dispensing fee):
- **Naproxen 375mg PO BID (~ $16)**
- **Meloxicam 7.5mg PO OD (~ $32)**
- **Celecoxib 200mg PO OD (~ $52)**
- **Rofecoxib 12.5mg PO OD (~ $52)**

## MELOXICAM (Mobicox®)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug &amp; Dose</th>
<th>Duration</th>
<th># pts</th>
<th>Any GI adverse event – 28 days (dyspepsia, etc.)</th>
<th>Perforations or Bleeds - 28 days</th>
<th>Perforations, Ulcers, or Bleeds (PUBs) - 28 days</th>
<th>Any event causing DC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELISSA 8</td>
<td>Meloxicam 7.5mg OD, Diaclofenac 100mg SR OD</td>
<td>28 days OA</td>
<td>4635/4688</td>
<td>13%/19% (p&lt;0.001)</td>
<td>0/4 not significant</td>
<td>0.1%/0.15% not significant</td>
<td>7.2%/9% (p=0.0014) (due to ADR or efficacy)</td>
<td><em>higher hospitalization rate in diclofenac group; more pts age &gt;65 &amp; pts with hx of PUBs; more pts in meloxicam group discontinued due to lack of efficacy but less due to adverse reactions.</em></td>
</tr>
<tr>
<td>SELECT 9</td>
<td>Meloxicam 7.5mg OD, Piroxicam 20mg OD</td>
<td>28 days OA</td>
<td>4320/4336</td>
<td>10.3%/15.4% (p&lt;0.001)</td>
<td>0/4 not significant</td>
<td>0.16%/0.37% not significant</td>
<td>6.13%/7.24% (p=0.06) NS</td>
<td><em>piroxicam group: more &gt;65yo; but less with a hx of PUBs; withdrawals due to GI adverse events less with meloxicam vs piroxicam (3.79% vs 5.26%) p&lt;0.01%</em></td>
</tr>
</tbody>
</table>

### What we know:
- *Meloxicam was better tolerated and caused fewer withdrawals due to GI adverse events than non-selective NSAIDs.*
- *Whether meloxicam significantly reduces the risk of complicated and symptomatic ulcers compared to non-selective NSAIDs cannot be determined from these trials; differences shown in these studies were not statistically significant and the low-dose (1/2 usual maximum) and short duration (28 days) of the studies makes interpretation difficult.*

### What we don’t know:
- Whether the safety profile would be significantly improved in patients on a usually recommended or lowest effective dose as opposed to supratherapeutic doses from trials.

### Meloxicam long-term data:
- *Study 024: ulcer complication rate of 0.23% (≤2 years exposure); postmarketing surveillance incidence of ulcer complications <0.02%; 30 fatal GI events in 1999; acute renal failure 0.0039%.
- *Rofecoxib long-term data: Study 024: ulcer complication rate of 0.23% (≤2 years exposure); postmarketing surveillance incidence of ulcer complications <0.02%; 30 fatal GI events in 1999; acute renal failure 0.0039%.*

## CELECOXIB (Celebrex®) & ROFECOXIB (Vioxx®)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug &amp; Dose</th>
<th>Duration</th>
<th># pts</th>
<th>Any GI adverse events</th>
<th>GI ulcer complications / 100 pt-yrs</th>
<th>GI ulcer complications + symptomatic ulcers / 100 pt-yrs</th>
<th>Any event causing DC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS 11</td>
<td>Celecoxib 400mg BID, Ibuprofen 800mg TID, Diclofenac 75mg BID</td>
<td>≤56mo; ave 4.2mo NS OA or RA</td>
<td>3987/1985/1996</td>
<td>45.6%/46.2%/55.0% (p&lt;0.05)</td>
<td>0.76/1.45/1.27 (p=0.09) NNT=120</td>
<td>2.08/3.54/2.91 (p=0.02) NNT=68.5</td>
<td>22.4%/23.0%/26.5% NS</td>
<td>• <em>Dose of celecoxib 2X usual max daily dose</em>; • <em>Only 4573 completed full 6 month trial; high drop out rate</em>; • <em>&gt; withdrawal rate due to GI ADR in diclofenac group (16.6% vs 12.2% for celecoxib) may have underestimated its GI risk</em>; • <em>Differences in GI ulcers/complications were found for celecoxib versus ibuprofen (2.08 vs 4.31/100 pt-yrs; p=0.005) but not celecoxib vs diclofenac (possibly due to &gt; withdrawal rate)</em>; • <em>Pts at ↑ risk for GI events also had ↑ withdrawal rates</em>; • <em>Fewer celecoxib pts had GI blood loss, GI intolerance</em>; • <em>No difference in CV events (but ASA allowed in study)</em>; • <em>Celecoxib arm had more pts &gt; 65yo &amp; hx of upper GI bleeds</em>; • <em>Rash with high-dose celecoxib (6.2%); appears to be dose-dependent ↑ from previous data; (sulfa allergy pts excluded)</em>**</td>
</tr>
</tbody>
</table>

| Subgroup: as above but excluding patients on ASA ≤325mg/d | ASA appeared to be an independent cause of ulcers in celecoxib pts, but not for NSAIDs (RR =4.5). | 0.44/1.27/1.04 (p=0.09) NNT=120 | 0.57/3.54/2.91 (p=0.02) NNT=68.5 | 2.01/4.7/4.01 (p=0.49) NNT=66 | 22.4%/23.0%/26.5% NS | • *Dose of celecoxib 2X usual max daily dose*; • *Acute MI > in rofecoxib than naproxen (0.5% vs 0.1%)*; • *DC due to hypertension > in rofecoxib (0.7% vs 0.1%)*; • *HTN & edema appear to be dose dependent (previous data)*; • *DC due to GI ADR lower in rofecoxib (RR = 0.73; p<0.001)*; • *Similar incidence of rash (rofexicib vs naproxen 3.5% vs 3%)*; • *Better GI safety but some adverse outcomes related to non-GI events; ASA pts excluded; *rofexicib arm had less pts age >65*** |

| Subgroup: as above but including patients on ASA ≤325mg/d | ~22% of each treatment arm had concurrent ASA | 2.01/4.7/4.01 (p=0.49) NNT=66 | 2.01/4.7/4.01 (p=0.49) NNT=66 | 2.01/4.7/4.01 (p=0.49) NNT=66 | 22.4%/23.0%/26.5% NS | • *Dose of celecoxib 2X usual max daily dose*; • *Acute MI > in rofexicib than naproxen (0.5% vs 0.1%)*; • *DC due to hypertension > in rofexicib (0.7% vs 0.1%)*; *ASA would be an independent cause of ulcers in celecoxib pts, but not for NSAIDs (RR =4.5).* |

| VIGOR 12 | Rofecoxib 50mg OD, Naproxen 500mg BID | ≤13mo; mean 8mo RA | 4047/4029 | 32.6%/36% | 0.59/1.37 (p=0.005) NNT=128 | 2.08/4.49 (p=0.001) NNT=41.5 | 15.9%/15.8% NS | • *Dose of rofexicib 2X usual max daily dose*; • *Acute MI > in rofexicib than naproxen (0.5% vs 0.1%)*; • *DC due to hypertension > in rofexicib (0.7% vs 0.1%)*; • *HTN & edema appear to be dose dependent (previous data)*; • *DC due to GI ADR lower in rofexicib (RR = 0.73; p<0.001)*; • *Similar incidence of rash (rofexicib vs naproxen 3.5% vs 3%)*; • *Better GI safety but some adverse outcomes related to non-GI events; ASA pts excluded; *rofexicib arm had less pts age >65*** |

### What we know:
- *Rofexicib reduced the risk of complicated &/or symptomatic ulcers but increased the risk of acute MI compared to the non-selective NSAID, naproxen.*
- *Celecoxib significantly reduced the risk of complicated &/or symptomatic ulcers compared to ibuprofen.*
- *Risk of serious ulcer complications in patients on celecoxib and low-dose ASA was not significantly different from those on non-selective NSAIDs and ASA.*

### What we don’t know:
- *Whether risk of serious GI toxicity in patients on rofexicib and ASA would be reduced compared to patients on non-selective NSAIDs and ASA.*
- *Whether the safety profile would be significantly improved in patients on a usually recommended or lowest effective dose as opposed to supratherapeutic doses from trials.*
- *Whether COX-2 selective agents are significantly safer in high-risk patients (e.g. the very elderly ≥75yo or patients with previous hx of ulcers).* • *How the selective COX-2 agents compare to each other in terms of overall safety or efficacy. (No head-to-head trials; different trial designs.)*

### Celecoxib long-term data:
- *Study 024: ulcer complication rate of 0.23% (≤2 years exposure); postmarketing surveillance incidence of ulcer complications <0.02%; 30 fatal GI events in 1999; acute renal failure 0.0039%.*

### Rofexicib long-term data:
- *Postmarketing surveillance - 59 complicated PUBs in 1999 (but only approved May/1999); complicated upper GI events = 0.014 per 100 pt-yrs; Background rate of ulcers: estimated to be approximately 0.1 to 0.4 events per patient years (varying as function of patient age); general ulcer rate for NSAIDs is thought to be ~2-4% per year; risk ↑ with ↑ dose; acute renal failure secondary to NSAIDs = 15-20 per 100 000 pt-yrs; NSAIDs account for 16,500 deaths/year in the USA.*

### Of interest, MUCOSA study:
- *Misoprostol (200mcg po qid) ↓ the rate of serious complicated upper GI events from 0.95% to 0.56% for NSAID users with RA over 6 months (ARR =0.4%; NNT=250).*

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**Notes:**
- OA = osteoarthritis; RA = rheumatoid arthritis; y = years old; NS = not (statistically) significant; GI = gastrointestinal; ADR = adverse drug reaction; CV = cardiovascular; pts = patients; hx = history.
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<thead>
<tr>
<th>Standard Size – Drug Comparison Charts</th>
<th>Pocket Size – Drug Comparison Charts</th>
</tr>
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<td>Small Book / Very Small Print ~ 5.5” x 7.5”</td>
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<td><strong>Quantity</strong></td>
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