FDA Risk/Benefit Considerations

Eric Bastings, MD
Clinical Team Leader
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Background

- Naproxen sodium 500 mg and metoclopramide hydrochloride 16 mg
- Proposed indication: acute treatment of migraine headache with or without aura
- Not approvable action (5/28/04) – contribution of both active drug components to the claimed effects of the product not established

Combination policy (CFR 300.50)

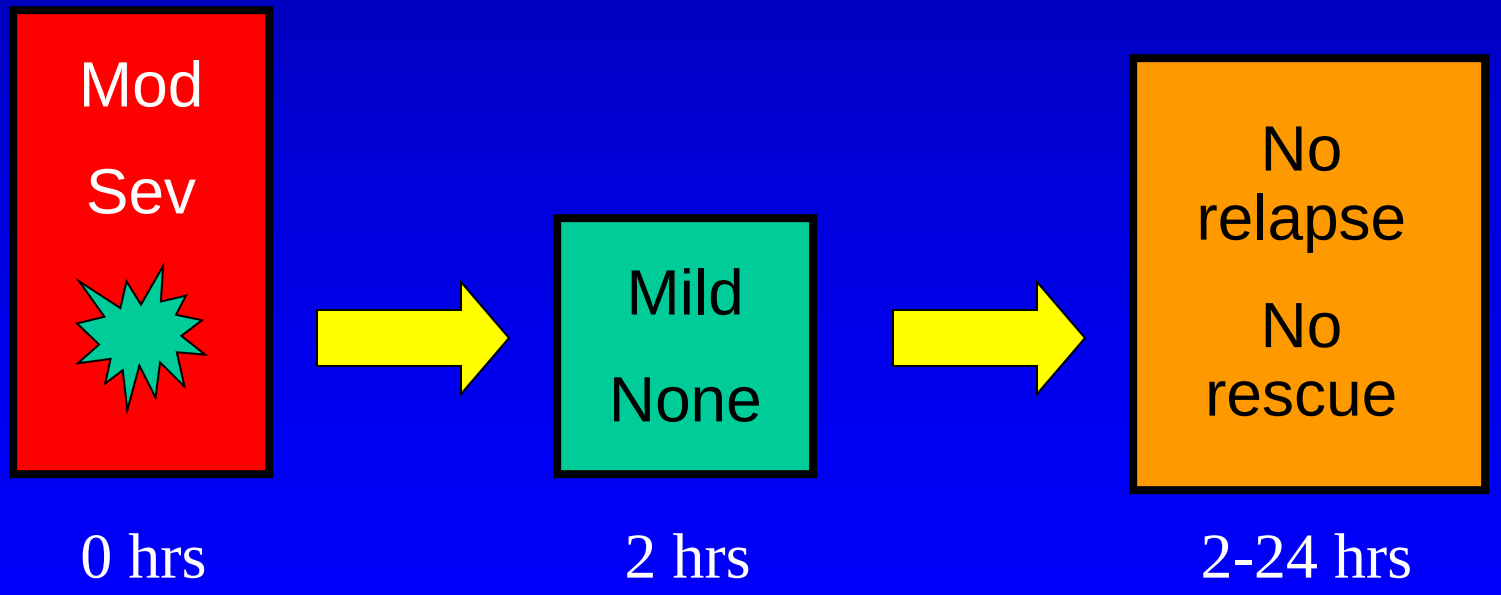
- Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Combination policy – MT100

- Factorial studies of similar design : MT100-301 and MT100-304
- Patients randomized to MT100, naproxen or metoclopramide
- Primary endpoint for combination policy: Sustained Pain Response.

Sustained Pain Response

- Moderate or severe headache pain at baseline
- Mild or no headache pain at 2 hours
- No relapse, no use of rescue medication 2-24 h



Sustained Pain Response: no significant contribution of metoclopramide

Study	MT100	Naproxen	Metoclopramide contribution ∫
301 (n=1067)	35.6%	29.8%	5.8% (p=0.064)§
304 (n=2627)	31.8%	27.9%	3.9% (p=0.063) §

∫ Metoclopramide contribution to MT100 response = MT100 response minus naproxen response.

§ FDA analysis

2-hour Endpoints in Factorial Studies§ (not required to establish metoclopramide contribution)

Endpoint (%)	MT100-301		MT100-304	
	MT100	Naproxen	MT100	Naproxen
2-hr pain response	48.1	46.6 p=0.67	49.8	46.7 p=0.14
2-hr Nausea	23.7	26.6 p=0.33	33.7	36.7 p=0.14
2-hr Photophobia	54.5	52.2 p=0.50	54.8	53.9 p=0.72
2-hr Phonophobia	45.7	48.0 p=0.50	48.0	48.1 p=0.98

§ Pozen analysis

2-hour Pain Response, Responder Relapse or Rescue Medication Use in Study 301§

Endpoint (%)	MT100	Naproxen	Metoclopramide contribution
2-hr Pain Response	48.1	46.6 [a]	1.5
Relapse or Rescue¥	12.6	16.8	4.2
Sustained Response	35.6	29.8 [a]	5.8

§ Pozen analysis

[a] Not statistically significant

¥ (After response at 2-hours)

2-hour Pain Response, Responder Relapse or Rescue Medication Use in Study 304§

Endpoint (%)	MT100	Naproxen	Metoclopramide contribution
2-hr Pain Response	49.8	46.7 [a]	3.1
Relapse or Rescue¥	17.9	18.8	0.9
Sustained Response	31.8	27.9[a]	3.9

§ Pozen analysis

[a] Not statistically significant

¥ (After response at 2-hours)

Associated Symptoms Sustained Responses in Factorial Studies (not required to establish metoclopramide contribution)

Endpoint (%)	MT100-301		MT100-304	
	MT100	Naproxen	MT100	Naproxen
Sustained Nausea Free	45.3	39.4 p=0.10	37.0	33.5 p=0.08
Sustained Photophobia free	32.2	29.8 p=0.41	27.9	27.0 p=0.58
Sustained Phonophobia free	35.3	30.3 p=0.17	32.3	29.3 p=0.14

Post-Action Meeting (Oct 6, 2004)

- Presentation of exploratory subgroup analyses suggesting a contribution of metoclopramide in patients with no nausea at baseline (no pre-specified plan for correction for multiple comparisons)
- Consideration by FDA of the acceptability of a prospective replication of these findings to fulfill the combination policy requirements

Subgroup Analyses in Study 301 (nausea present or absent at baseline)*

Endpoint (%)	All patients		No nausea at baseline		Nausea at baseline	
	MT100 (n=423)	Naproxen (n=430)	MT100 (n=231)	Naproxen (n=233)	MT100 (n=192)	Naproxen (n=197)
Sustained Pain Response	35.6	29.8 p=0.064	38.4	28.5 p=0.009	32.3	31.5 p=0.78
2-hr Pain response	48.1	46.6 p=0.665	50.7	45.3 p=0.40	45.3	48.2 p=0.59

*Pozen analysis

Subgroup Analyses in Study 304 (nausea present or absent at baseline)*

Endpoint (%)	All patients		No nausea at baseline		Nausea at baseline	
	MT100 (n=1036)	Naproxen (n=1062)	MT100 (n=342)	Naproxen (n=361)	MT100 (n=694)	Naproxen (n=701)
Sustained Pain Response	31.8	27.9 p=0.063	36.7	26.7 p=0.004	29.6	28.5 p=0.622
2-hr pain response	49.8	46.7 p=0.143	54.6	47.2 p=0.056	47.6	46.5 p=0.47

*Pozen analysis

Indication Limited to Patients with No Nausea at Baseline

- In a survey of 500 self-reported migraineurs*, nausea occurred in more than 90% of all migraineurs, and nearly one third of these experienced nausea during every attack.
- Only a minority of patients (<10%) consistently had migraine with no nausea at baseline (indication for which MT100 is being considered).
- 45-69% incidence of nausea at baseline in MT100 phase 3 studies

*Silberstein SD. Migraine symptoms: results of a survey of self-reported migraineurs. Headache. 1995 Jul-Aug; 35(7): 387-96.

Indication Limited to Patients with No Nausea at Baseline

Migraine patients (over 50% according to the Silberstein survey) may have some attacks with nausea, and other attacks without nausea, or nausea may develop during the attack.

Patients would therefore need two different treatments based on the presence or absence of nausea, or would treat their attacks with nausea with a combination product containing metoclopramide, which has no established contribution for efficacy for that type of attack, yet they would be exposed to the risks of metoclopramide.

Tardive Dyskinesia (TD)

- "Tardive" originally intended to emphasize late appearance during neuroleptic treatment
- TD may appear early during neuroleptic treatment*
- No fundamental distinction between cases appearing early and those appearing late. *

*In: Drug Induced movement disorder 2nd Ed. (Factor SA, Land AE, Weiner WJ, eds). Blackwell Futura, 2005.

Tardive Dyskinesia Variants

- Tardive dystonia (several cases with a few days of exposure to neuroleptics, including one non reversible case after a single dose)
- Tardive akathisia (may develop early)
- Tardive myoclonus
- Tardive tics
- Tardive tremor

Metoclopramide-induced Tardive Dyskinesia

- TD is a well known side effect of metoclopramide
- Exact incidence of metoclopramide-induced TD remains unclear.
- No case reported in MT100 database, but database too small to detect rare events.

TD Risks Associated to Chronic Metoclopramide Treatment.

- Metoclopramide WARNING: Tardive dyskinesia …/… may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop **after relatively brief treatment periods at low doses** [emphasis added]; in these cases, symptoms appear more likely to be reversible.

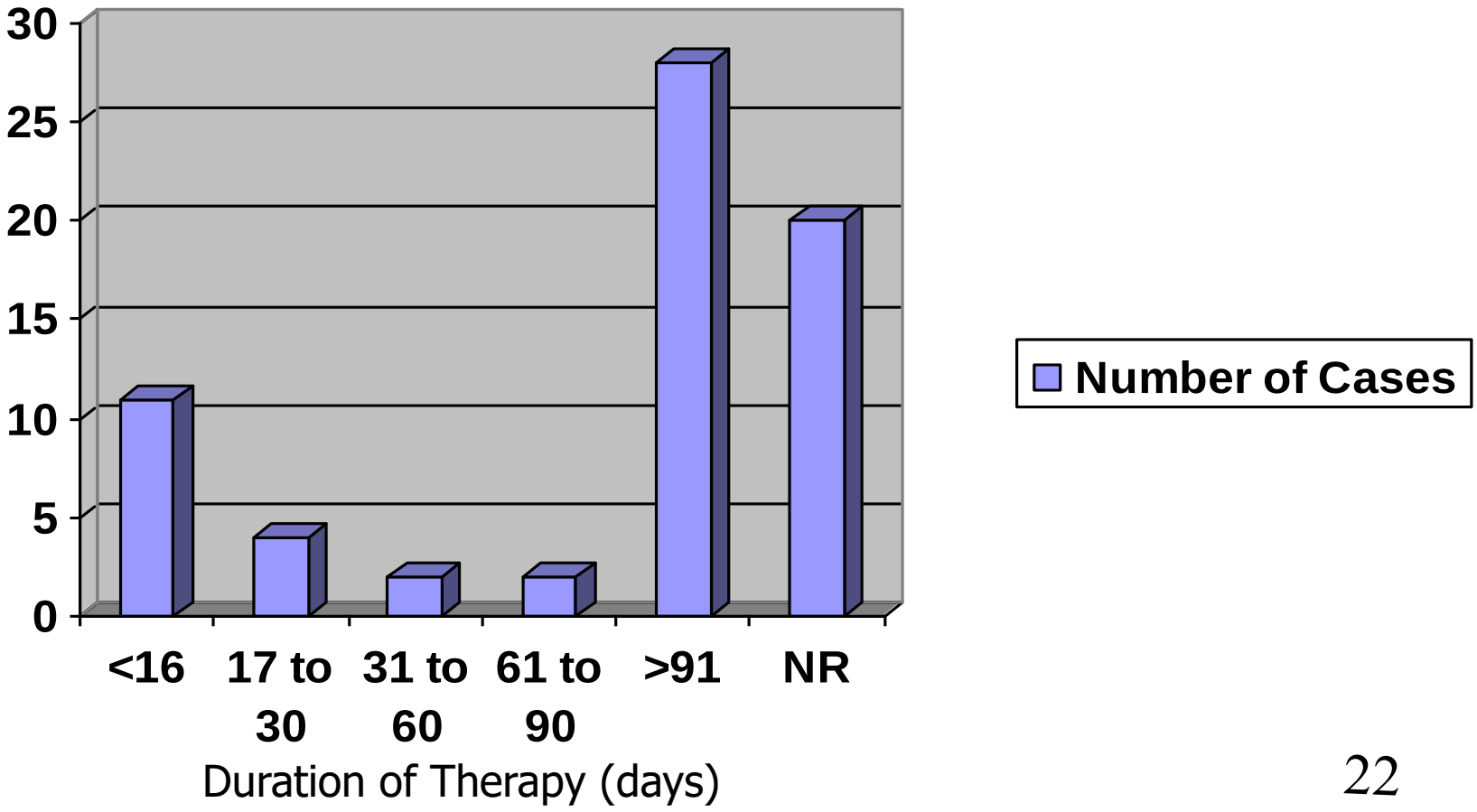
Metoclopramide: FDA-approved Indications

- Indicated for short-term therapy (4 to 12 weeks) of gastroesophageal reflux, only when conservative treatment fails, and for treatment of diabetic gastroparesis (2-8 weeks).
- Recommended dose 5 to 15 mg q.i.d.

TD Risks Associated with Chronic Metoclopramide Treatment.

- Cases reported in the literature after relatively short durations of treatment (1 week and more)
- Cases identified by FDA in the AERS database after short durations of treatment (1st quartile of TD cases = 29.5 days).

Distribution of TD cases Based on Duration of Therapy in AERS



Patterns of Use of Metoclopramide (IMS Health and Caremark)

- Metoclopramide mostly used (>50%) for GI indications (Esophagitis 40%); Migraine use <2%
- 13% of patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days; 7% of patients appeared to have received prescriptions for metoclopramide for over 180 days
- Over a 3-year period, cumulative therapy longer than 90 days for almost 20% of the patients; cumulative therapy for more than 180 days in >10% of patients.

Risk Associated with Chronic-intermittent (C-I) Use of Metoclopramide

- Difficult to evaluate: no current indication for C-I use, and no specific capture of C-I use in AERS.
- Animal data suggest intermittent use of neuroleptics may be no safer or even riskier than continuous use*
- In a psychiatric population, the number of interruptions in neuroleptic treatment was the second factor (after age) in predicting TD*

*Reference in introductory memorandum

Overuse of Acute Migraine Drugs

- "Medication-overuse" headache (MOH) introduced with 2004 IHS classification (8.2.3 analgesic-overuse headache)
- "Substantial evidence" that all drugs used for the treatment of migraine may cause MOH*
- MOH prevalence in general population around 1% ¥
- Overuse of symptomatic migraine drugs and/or analgesics most common cause of chronic daily headache, according to the IHS*

* In: Chronic daily headache for clinicians (PJ Goadsby, SD Silberstein, DW Dodick eds.). BC Decker, 2005. ¥ Reference in introductory memorandum.

Question 1

Pozen estimated an annual incidence of tardive dyskinesia (TD) of up to 0.038% for metoclopramide at a daily dose of 30-40 mg/day for 72 days/year (which corresponds to up to 380 cases of TD per million patients per year).

Do you think that this is a reasonable estimate?

If MT100 were to carry the same risk, would such a risk level be acceptable if the only contribution of metoclopramide is a 5-10% improvement on sustained headache relief (with no effect on 2-h endpoints)?

Is any risk of tardive dyskinesia acceptable for a migraine population?

Question 2

Is there sufficient evidence that the chronic-intermittent administration of metoclopramide does not carry a risk of tardive dyskinesia?

Is it possible to define a maximum recommended number of monthly doses of MT100 to avoid the risk of tardive dyskinesia?

Question 3

Do you believe that, based on the existing data on medication-overuse headache, there is evidence that a proportion of patients prescribed MT100 will likely take a number of monthly doses higher than recommended?

Question 4

All currently approved acute treatments of migraine are indicated without restriction regarding the presence or absence of nausea at baseline.

Given that patients may have nausea at some attacks and no nausea at others, does an indication limited to the subpopulation of migraine patients with no nausea at baseline represent a clinically meaningful and acceptable indication?

Question 5

If Pozen shows prospectively in a new clinical study in migraine patients with no nausea at baseline:

- a significant contribution of metoclopramide on sustained headache pain relief of 5-10%
- no contribution of metoclopramide at 2-hours
- no contribution of metoclopramide on relapse rate or rescue medication use in the 2-24 hour period,

Would the demonstrated benefit outweigh the risks related to tardive dyskinesia?

If not, what additional data (or desired primary outcome, or desired effect on sustained relief) could provide evidence of safety and efficacy?

Acknowledgements

- Marc Avignan, M.D., C.M.
- Yeh-Fong Chen, Ph.D.
- Gerald Dal Pan, M.D., M.H.S.
- Kun Jin, Ph.D.
- Sigal Kaplan, Ph.D., B. Pharm.
- Russell Katz, M.D.
- Cindy Kortepeter, Pharm.D.
- Susan McDermott, M.D.
- Kevin Prohaska, D.O.
- Judy Racoosin, MD, M.P.H.
- Mary Ross Southworth, Pharm.D.
- Barry Rosloff, Ph.D.
- Judy Staffa, Ph.D., R.Ph.
- Robert Temple, M.D.