
MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Date: May 18, 2004
From: Eric Bastings, MD.
To: Russell Katz, MD
Subject: 21-645 Myzan (MT100)

This submission is a new drug application (NDA) for the use of MYZAN (previously MT100) for the intermittent treatment of acute migraine with and without an aura in adults. MYZAN is a combination product consisting of a metoclopramide hydrochloride monohydrate (16 mg/tablet) shell, and naproxen sodium (500 mg/tablet) central core.

For this NDA, Josephine Jee provides the chemistry review, Dr. Kathleen Haberny provides the pharmacology/toxicology review, Dr. Kofi A. Kumi provides the clinical pharmacology review, Dr. Yeh-Fong Chen provides the statistical review and Dr. Kevin Prohaska provides the clinical review. Jerry Phillips provides a consultative review of the drug name, carton, and container for the Division of Medication Errors and Technical Support. Jeanine Best from ODS provides a review of the patient insert labeling. Dr. Ni Khin provides the DSI review.

Chemistry, Manufacturing and Controls (CMC)

Josephine Jee recommends approval from a CMC perspective.

Pharmacology/Toxicology

As noted by Dr. Haberny and by Dr. Barry Rosloff (Pharm/Tox team leader), Pozen was required to conduct a two year rat carcinogenicity study. MT 100 caused increased incidences of mammary tumors, adrenocortical tumors, pheochromocytomas, and pancreatic islet cell tumors. Pozen postulates that all of these tumors result from the increased levels of prolactin known to be produced by metoclopramide, and Dr. Rosloff agrees that this is presumably the case, although there are inadequate data to fully support this assertion.

Even if prolactin as a mechanism for carcinogenicity is accepted, there is no evidence that it would not be operative in humans. Metoclopramide is known to increase prolactin at therapeutic doses in humans, and is even cited as the galactologue of choice in the literature¹. If prolactin is indeed the cause of the tumors, the increased prolactin level reported with therapeutic doses of metoclopramide in the human is not a comforting observation. Dr. Rosloff notes that most dopamine-blocking antipsychotic drugs produce

¹ Gabay MP. Galactogogues: medications that induce lactation. J Hum Lact. 2002; Aug; 18(3): 274-9.

mammary tumors in rodents but as a class are not thought to produce mammary tumors in humans. However, Dr. Rosloff cites a more recent study which suggested a small but significant risk of breast cancer with dopamine antagonists in the human².

Assuming a non-genotoxic mechanism, Dr Rosloff believes that there is somewhat of a safety margin with respect to expected human plasma levels of metoclopramide (except for female mammary tumors, where there was no clear NOEL established). On the other hand, the proposed human administration is meant to be intermittent, which lowers the risk for a non-genotoxic carcinogen (with the caveat that some patients will probably use the drug chronically even if labeling recommends intermittent use). Also, Dr. Haberny and Dr. Rosloff remind of the context of other drugs used in migraine, several of which have carcinogenicity findings described in the labeling.

Clinical Pharmacology and Biopharmaceutics

Dr. Kumi recommends approval. The pharmacokinetics of naproxen and metoclopramide were considered bioequivalent following administration of the MT 100 formulation versus the individual naproxen and metoclopramide components. Metoclopramide pharmacokinetics were unaffected by a migraine attack, but naproxen AUC and C_{max} were slightly reduced (10- 15%). There was a slight food effect for naproxen and metoclopramide pharmacokinetics, with T_{max} delayed by approximately 1 hour for both drugs, and naproxen C_{max} reduced by approximately 24% by administration with food. In patients with moderate hepatic impairment, metoclopramide pharmacokinetics were similar to those of healthy subjects and total naproxen AUC increased by 27%. However, the AUC and C_{max} of unbound naproxen increased by greater than 2- fold in subjects with hepatic impairment compared to healthy subjects. Because of increased exposure to naproxen, particularly unbound naproxen, Dr. Kumi recommends that MT 100 should be used with caution in patients with hepatic impairment. Dr. Kumi also recommends that MT 100 is not administered to patients with creatinine clearance below 40 mL/min (this is based on metoclopramide labeling recommendations; no study was conducted in patients with renal impairment). OCPB made several labeling, dissolution and specifications recommendations. However, since my final recommendation is a non approval action, these recommendations will not be implemented in this review cycle.

Clinical and Biostatistics

Dr. Kevin Prohaska and Dr. Yeh-Fong Chen recommend non-approval. According to the combination policy [CFR 300.50 (a)], 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. Pozen has not met the combination policy requirement for MT100, and has not established that both active drug components make a contribution to the claimed effects. Special cases of this general rule are where a component is added to enhance the safety or effectiveness of the principal active component, or to minimize the potential for

² Wang PS, et al. Dopamine antagonists and the development of breast cancer. J. Arch Gen Psychiatry. 2002 Dec; 59(12): 1147-54.

abuse of the principal active component. MT100 does not correspond to either of these special cases.

Two factorial studies explored the contribution of individual components to the safety and efficacy of the combination: Study MT100-301 and -304. I concur that both studies demonstrate a clear benefit of the combination over metoclopramide for the sustained headache pain response, but both studies fail to demonstrate a benefit of the combination over naproxen. The primary endpoint for the two factorial studies was sustained headache response (defined as moderate to severe headache pain at baseline going to no or mild pain at 2 hours and did not relapse or require rescue medication up to hour 24). The following table (copied from table 3 of Dr. Prohaska review, page 10) summarizes the primary endpoint results for the factorial studies:

Sustained Pain Response (any response) in MT100-301 and MT100-304

Trial	MT100 n(%)	Naproxen 500 mg n(%)	Metoclopramide 16 mg n(%)
MT100-301 N=1067	150 (35.6%)	128 (29.8%) p=0.077*‡	42 (19.7%) p<0.001*‡
MT100-304 N=2627	328 (31.8%)	295 (27.9%) p=0.038*‡ (p=0.063)?	99 (18.8%) p<0.001*‡

Adapted from sponsor table 23 study report MT100-301 and amended table 27 study report MT100-304 (paper submission 1/14/04).

*p-values from the sponsor's analysis for comparison of MT100 versus individual components using prestated analysis plan from both studies (Trial 301 logistic regression, trial 304 CMH). According to FDA analysis, p-value was 0.064.

‡ using post hoc ordered logistical regression, MT100 vs. naproxen p=0.025 and MT100 vs. metoclopramide p<0.001. Source sponsor table 5, study report 301.

‡ using post hoc ordered logistical regression, MT100 vs naproxen p=0.030 and MT100 vs. metoclopramide p<0.001. Source sponsor table 5 and 27 (original report), study report 304.

? p-value from Agency Statistician's analysis who reports sponsor's analysis had a programmatic error.

Both studies failed to reach statistical significance for the primary endpoint analysis in the comparison of MT100 and naproxen. It is important to briefly discuss here the differences between the analysis conducted by the sponsor and these conducted by FDA.

For Study 301, Pozen tried to use a post-hoc "refinement analysis" (ordered logistic regression with baseline pain and investigator site as the covariates) instead of the a priori designated logistic regression. The use of the "refined" analysis led to a statistically significant difference between MT100 and naproxen (p=0.025). In a 3/27/00 telecon with Pozen (minutes of which are filed in DFS and were sent to the sponsor), the division notified Pozen that FDA does not agree that Study 301 is positive on its primary endpoint, "sustained response" because Pozen performed a "refinement" to the analysis which was not prespecified, and was performed after the data were unblinded. Pozen proposed using an "almost positive" Study 301 and a positive second study to demonstrate superiority of MT100 over its components and then using other trials to demonstrate efficacy over placebo. The division agreed to this approach but also reminded Pozen that the division would be looking at improvements in the secondary outcome measures of nausea, photophobia, and phonophobia in order to establish efficacy.

For Study 304, as discussed by Dr. Chen on page 16 of her review, and according to the study report, Pozen used ordered logistic regression (with baseline pain and investigator site as covariates) to test MT100 versus naproxen, and MT100 versus metoclopramide. Using that analysis, MT100 was significantly better than both naproxen ($p=0.03$) and metoclopramide ($p<0.001$). However, Dr Chen (and Dr. Prohaska) found that ordered logistic regression was not the sponsor's protocol specified primary method. The protocol specified method was the extended Mantel Haenszel statistic with score of 0, 1, and 2 for the three ordered categories (no sustained pain relief, sustained pain relief, and sustained pain free), and using a model that controls for center, baseline pain and gender. Pozen was informed of this discrepancy during the NDA review cycle, and asked to reanalyze the data according to the pre-stated analysis plan. Pozen's reanalysis showed a slightly higher p- value for comparison of MT100 to naproxen ($p=0.038$ versus $p=0.030$). Pozen concluded that the interpretation of the statistical significance of the results remains the same. As discussed by Dr. Chen on page 22 of her review, Pozen performed this analysis using a SAS macro written by Koch. Dr. Chen requested that Pozen submits to the division the program and the SAS macro, and then evaluated Pozen's analysis results. Dr. Chen found that by using the SAS macro written by Koch, the p- value for the comparison between MT100 and naproxen is 0.063 and not 0.038. Dr. Chen noted that Pozen mistakenly used equal weight for all strata in their analysis, instead of a weight that is comparable to the stratum's proportion of patients in the trial.

To further evaluate the study results, Dr Chen also analyzed the data by stratifying the center factor only, which is the only factor usually stratified. This led to a non significant difference between MT100 and naproxen ($p=0.09$), both with the Koch's SAS macro or with Dr. Chen's SAS program. In addition to the lack of a statistically significant difference between MT100 and naproxen in the factorial studies, the treatment effect size (for sustained relief) of MT100 over naproxen is clinically marginal (4-6%). The trend for statistical significance despite the small treatment effect size is probably explained by the very large sample size of the factorial studies (i.e. $n=2627$ in Study 304), much larger than for typical migraine studies. In that sense, the studies (and especially Study 304) were apparently overpowered. As discussed by Dr. Prohaska on page 10 of his review, the lack of benefit of MT100 over naproxen is further supported by the fact that MT100 was not statistically different from naproxen for all key symptoms at the 2-hour endpoints typically used in migraine trials, and for sustained nausea-free, photophobia-free and phonophobia-free (as detailed in the following table, copied from page 11 of Dr. Prohaska review).

Selected Secondary Endpoint Results from Trials MT100-301 and MT100-304

Parameter	MT100-301			MT100-304		
	MT100	NAP	MET	MT100	NAP	MET
2-hr pain response (%)	48.1	46.6 p=0.665	34.3 p<0.001	49.8	46.7 p=0.143	36.6 p<0.001
2-hr pain free (%)	18.7	14.0 p=0.053	9.4 p=0.002	16.8	16.0 p=0.604	9.1 p<0.001
2-hr Nausea^ε (%)	23.7	26.6 p=0.333	25.4 p=0.646	33.7	36.7 p=0.138	41.5 p=0.003
2-hr Photophobia^ε (%)	54.5	52.2 p=0.504	63.4 p=0.033	54.8	53.9 p=0.721	62.1 p=0.007
2-hr Phonophobia^ε (%)	45.7	48.0 p=0.504	52.1 p=0.129	48.0	48.1 p=0.983	52.8 p=0.080
Sustained Nausea Free (%)†	45.3	39.4 p=0.100	30.5 p<0.001	37.0	33.5 p=0.083	26.7 p<0.001
Sustained Photophobia Free (%)†	32.2	29.8 p=0.409	19.7 p<0.001	27.9	27.0 p=0.584	21.0 p<0.003
Sustained Phonophobia Free (%)†	35.3	30.3 p=0.174	22.5 p<0.001	32.3	29.3 p=0.135	21.4 p<0.001

The lack of a demonstrated benefit of the combination over its components is sufficient, in my opinion, to justify a non approvable action. There are however additional efficacy and safety issues, as discussed below. The sponsor conducted three key efficacy studies (MT100-306, -308 and -303) comparing MT100 to placebo in all three studies, and to Imitrex 50 mg as an active comparator in two studies (MT100-306 and -308).

Study 306 can be considered as an almost positive study. For the comparison to placebo (primary comparison), MT100 was statistically superior to placebo for the key symptoms of pain response, nausea, and photophobia at 2 hours. However, the comparison did not reach statistical significance for phonophobia, but trended strongly (p=0.06 by the sponsor analysis, and p=0.052 by FDA analysis). I believe that this study could be used to support a migraine claim for MT100 if a second study showed efficacy on all key symptoms of migraine at 2 hours (with the remaining obligation to address the combination rule).

Study 308 is, in my opinion, a negative study. In Study 308, the primary comparison was for equivalence to sumatriptan. As discussed by Dr. Chen in page 40-41 of her review, the division did not agree with the analysis plan and informed Pozen of that disagreement long before the NDA was filed (in a 6/8/01 email). Specifically, the division identified three problems: the sponsor did not plan to compare MT100 with the entire approved therapeutic range for Imitrex, the analysis plan failed to define what margin of difference would be acceptable to determine equivalence, and the comparison did not include the key migraine associated symptoms. Pozen proposed a margin for non inferiority, which the division did not agree to, and did not address the other two issues. Therefore, as concluded by Dr. Chen, the non- inferiority comparison is not acceptable. For that reason, I will not discuss the comparison to sumatriptan further, and I will only consider the comparison to placebo.

In the comparison of MT100 to placebo, the p-values are below 0.05 for migraine pain ($p=0.001$) and photophobia ($p=0.044$), but above 0.05 for nausea and phonophobia. Dr Chen expresses some additional concerns for the comparison of MT100 to placebo, because this was a secondary comparison, and because the study was overpowered. In my opinion, since the division rejected the primary comparison to sumatriptan before seeing any result of the study, it is reasonable to consider the comparison to placebo as the primary comparison. For pain relief, the treatment effect size of 12% is in the lower end of effect sizes observed for acute migraine treatment, but appears large enough to overcome the concern for a significance difference mostly supported by overpowering the study. For photophobia however, the effect size is marginal (8%). In addition, since all key endpoints did not win against placebo, I believe that a correction for multiple comparisons must be used to interpret the individual key associated symptoms analysis. I believe that the significance ($p=0.044$) of the comparison of photophobia between MT100 and placebo would not be sustained after correction for multiplicity. Overall, I believe that this trial shows a superiority of MT100 over placebo for migraine pain only, which comes short of an acute migraine treatment claim.

The third pivotal efficacy trial, Study MT100-303, was also a negative study. For this study, the primary comparison was between MT100 and placebo, and used sustained pain relief instead of the typical 2-hour endpoints. Pozen can be commended for randomizing non responders at 2 hours to a second dose of MT100 or placebo, which was a secondary comparison. According to the study report, ordered logistic regression analysis of the sustained pain response data demonstrated that an initial dose of MT100 was significantly better than placebo ($p=0.048$). Dr. Chen however reanalyzed the data and got a p-value of 0.062. According to the sponsor's second and last protocol amendment, the 2-hour sustained response data were to be analyzed by ordered logistic regression controlling for center, baseline severity and gender. Dr. Chen (see page 49 of her review) found that Pozen's p-value (0.048) was actually obtained from an ordered logistic regression model that did not include any covariates, although the study report mentioned the baseline pain and investigator site as covariate. In addition, according to the last version of the study protocol, there were two primary endpoints: the 2-hour sustained response for subjects initially randomized to MT100 or placebo and the 4-hour sustained response for MT100 non-responders randomized to a second dose of MT100 or placebo. Pozen, however, did not specify that the 4-hour sustained response was the second primary endpoint in the study report, and did not propose any multiple comparison method for preserving the type I error rate. This observation strengthens the above conclusion that this study was negative. Also, there was no evidence to support the efficacy of a second dose of MT100 in non-responders.

Regarding the safety of MT100, my main concern relates to the extrapyramidal adverse events known to be caused by metoclopramide³. Reglan labeling states that extrapyramidal symptoms, mainly acute dystonic reactions, occur in approximately 0.2% of patients receiving oral metoclopramide at doses between 30 to 40 mg per day. Dr.

³ In a web search, I also found that metoclopramide manufacturers are apparently being sued for the tardive dyskinesia imputed to long term use of Reglan (see http://drugintel.com/reglan_tardive_dyskinesia.htm; <http://www.reglan-lawsuit.com>).

Prohaska notes that during the clinical development program for MT100, there were two subjects reporting acute dystonic reactions, which demonstrates the potential for extrapyramidal adverse events even at the dose (16 mg) of metoclopramide contained in MT100. Akathisia has also been reported with metoclopramide in the literature⁴, and metoclopramide-induced akathisia can even apparently lead to suicide attempt, as reported in the literature⁵.

Reglan labeling also states that tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. The label states that the risk increases with the duration of treatment and the cumulative dose. The literature supports that metoclopramide-induced tardive dyskinesia can be permanent⁶. That type of side effect can only be expected to be observed when large populations are exposed to the drug for a sufficient period of time, and not during the drug development program such as the one for MT100. In that sense, the absence of cases of tardive dyskinesia in the MT100 database is not indicative that this adverse reaction will not occur. Indeed, in an analysis of 67 cases of metoclopramide associated tardive dyskinesia, the mean length of treatment with metoclopramide before the onset of symptoms was 20 months⁷. In that study, the symptoms were still present 6 months or more after discontinuation of metoclopramide in most patients on whom long-term follow-up was provided. Tardive tremor due to metoclopramide was also recently described⁸. There is also a warning in Reglan labeling about a risk for depression, suicidal ideation and suicide. Finally, the label reports rare cases of neuroleptic malignant syndrome, which is potentially fatal.

In light of the concern with the CNS toxicity of metoclopramide, FDA has approved metoclopramide for short-term therapy (4 to 12 weeks) of gastroesophageal reflux, and only when conservative treatment fails. However, it is well known that labeling restrictions are not always followed by patients and practitioners, and that chronic use may occur despite labeling recommendations. Indeed, a published paper reports that 32% of metoclopramide users in a sample of elderly ambulatory patients used metoclopramide for longer than a year⁹. The exact incidence of metoclopramide-induced tardive dyskinesia remains unclear, but well known movement disorder experts have stated that to prevent persistent and disabling movement disorders, long-term use of metoclopramide should be avoided¹⁰. Two factors mitigating the risk of tardive dyskinesia in the case of

⁴ Akagi H, Kumar TM. Lesson of the week: Akathisia: overlooked at a cost. *BMJ*. 2002 22; 324(7352):1506-7.

⁵ Chow LY, Cung D, Leung V, Leung TF, Leung CM. Suicide attempt due to metoclopramide-induced akathisia. *Int J Clin Pract* 1997; 51: 330-331

⁶ Jeste DV, Caligiuri MP. Tardive dyskinesia. *Schizophr Bull*. 1993; 19(2):303-15.

⁷ Sewell DD, Jeste DV. Metoclopramide-associated tardive dyskinesia. An analysis of 67 cases. *Arch Fam Med*. 1992 Nov; 1(2): 271-8.

⁸ Tarsy D et al. *Mov Disord* 2002. 17 (3): 620-621.

⁹ Stewart RB, Cerda JJ, Moore MT, Hale WE. Metoclopramide: an analysis of inappropriate long-term use in the elderly. *Ann Pharmacother*. 1992; 26 (7-8): 977-9.

¹⁰ Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. *Arch Intern Med*. 1989 Nov; 149(11): 2486-92.

MT100 are the recommended chronic/intermittent use and the relatively low dose of metoclopramide. However, given the concern for permanent CNS toxicity, a robust clinical benefit is needed to justify the risks of MT100, especially for a migraine indication.

DSI

Overall, data quality appears acceptable. Four sites were inspected. Dr. Ni notes that various minor violations were observed in site (b) (4). I don't think these violations had any significant impact on the study. The most worrisome problem occurred in site (b) (4). In addition to some minor violations, there were discrepancies between data listings and data reported in diaries/electronic CRF (data were entered correctly in the electronic CRF from diaries) in most patients for the pain (b) (4) at various time points. The issue was however resolved. Following a meeting with Pozen identified the origin of the discrepancies as of an error in the production of the data listings generated for purposes of the FDA audit. Pozen also stated that the SAS transport files (SAS data sets) exactly matched the data in the electronic CRFs and that NDA data listings were correct (I do not believe that there were any significant deficiencies were noted in site (b) (4)). Finally, for site (b) (4), Pozen terminated the study based on findings from monitoring visits that the study coordinator changed the dates of administration of study drugs to reflect a date which would allow the follow-up visit to fall within the protocol required one to three day window. There were also issues with drug accountability records in this site. Dr. Prohaska reviewed the results with and without the data obtained from (b) (4) site and found no difference.

Drug name - Labeling

Kimberly Culley, from the Division of Medical Errors and Technical Services (DMETS) reviewed the drug name, carton, and container. DMETS does not recommend the use of the proprietary name, Myzan. The primary concerns relate to look-alike and sound-alike confusion with Zyban. Additionally, DMETS reviewed the container labels, carton and insert labeling from a safety perspective. DMETS has identified several areas of possible improvement, which I will not discuss further in this review cycle, because I am recommending a non approval action. Jeanine Best (Division of Surveillance, Research, and Communication Support) reviewed the patient insert. Ms. Best made a number of recommendations for changes: she simplified the wording, made it consistent with the PI, removed unnecessary information, and put it in the DSRC recommended format. Since I am recommending a non-approval action, I did not implement the changes in this review cycle.

Reviewers of various disciplines made labeling recommendations. Since I am recommending a non-approval action, I did not implement these labeling recommendations. They can be found in the discipline reviews.

Conclusions and Recommendation

I recommend a non-approvable action. There are a number of issues with this product.

First, Pozen has not met the combination policy requirement for MT100, and has not established that both active drug components make a contribution to the claimed effects of the product. In addition, the (non statistically significant) effect size of the combination over naproxen is clinically marginal (4-6% for sustained pain relief, no benefit for 2-hour outcomes typically used in migraine trials, and no sustained effect on nausea, photophobia and phonophobia).

Second, Pozen has not established the efficacy of MT100 in the acute treatment of migraine (only efficacy in treating headache pain was established). I note however that Pozen has an almost positive study for that effect (Study 306).

Third, there are safety concerns associated with the chronic use of metoclopramide. Metoclopramide is well known to induce not only acute dystonias, but also tardive dyskinesia, which can be permanent in some cases. Current labeling of metoclopramide and many papers in the literature recommend against a chronic use of the drug. Even though chronic use can be discouraged by labeling, some degree of chronic use is expected with patients or practitioners non compliant to the labeling.

Fourth, there are concerns about carcinogenicity associated with chronic use of metoclopramide. While there are a number of factors to consider in the interpretation of the carcinogenicity findings, this remains an important observation to integrate in the risk/benefit analysis of the product.

To support approval of MT100, I suggest the sponsor provides the following:

1. One positive factorial study with a clinically significant effect size. It will be important that this study is not overpowered.
2. One positive study showing effect on all migraine key symptoms at 2 hours. Of note, the factorial and the efficacy study could be combined into one single study, with the proper analysis plan.
3. A justification of the risk/benefit of MT100 in light of the extrapyramidal side effects associated to metoclopramide use, and to the carcinogenicity seen in the rat. In that sense, the clinical effect must be robust. In my opinion, even if statistical significance had been reached in all factorial and efficacy studies reported in this NDA, the effect sizes observed do not outweigh the safety concerns.

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/s/

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