Barry N. Rosloff, Ph. D.
5/14/04

NDA 21-645 (MT 100) – SUPERVISORY MEMO

I am in basic agreement with the analysis of and conclusions reached by Dr. Haberny (review of 5/13/04) regarding the preclinical data for MT 100.

MT 100 is a combination of two relatively old drugs, naproxen (NAP) and metoclopramide (MET). In addition to the usual practice of requiring a limited set of studies to look for potential drug interactions, we requested carcinogenicity studies, primarily because (1) there were studies indicating that both compounds were genotoxic, (2) there were no existing adequate carcinogenicity studies of MET, and (3) MET is structurally similar to sulpiride, a drug which was the subject of an old IND (9943) which was discontinued due to worrisome animal carcinogenicity findings (in addition to the mammary and pituitary tumors often seen with drugs of this class [i.e., blockers of dopamine receptors, usually indicated in schizophrenia], sulpiride caused pancreatic islet cell tumors, pheochromocytomas, lymphoid thymomas, and (equivocally) testicular interstitial cell adenomas (IND 9943, pharmacologist review of 3/4/82).

In the rat carcinogenicity study, MT 100 caused increased incidences of mammary tumors (benign as well as malignant in females; combined benign + malignant in males), adrenocortical tumors (benign as well as malignant in females; benign in males), pheochromocytomas (males only, benign), and pancreatic islet cell tumors (males only, malignant)*. The sponsor postulates that all of these tumors result from the increased levels of prolactin known to be produced by MET (and confirmed in the present study). However, with the possible exception of mammary tumors, there are inadequate data to support this assertion. The issue of rodent mammary tumors and prolactin has been dealt with by the Agency regarding other dopamine receptor blockers, and it has been considered that there is a reasonable basis for a causal association. The evidence is much less clear for the other tumor types seen (although it is noted that the labeling for oral risperidone does state that the endocrine pancreas tumors seen in rats are considered to be prolactin-mediated). Indirect evidence for a possible link is that these tumor types have occasionally been produced by other drugs which block dopamine receptors and/or increase prolactin (adrenal cortex-aripiprazole; pheochromocytomas-risperidone, sulpiride; endocrine pancreas-risperidone, sulpiride, sertindole, chlorpromazine, penfluridol, amoxapine), although of course it should be noted that these drugs have other actions in common besides increasing prolactin. Within the MT 100 rat study, there was not always a tight correlation between group mean prolactin levels and tumor incidence values, e.g. tumor incidences in the high dose combo group were generally greater than those in the MET-alone group despite similar prolactin levels. No clear ancillary evidence implying stimulation of the endocrine glands in question (e.g. changes in ACTH, adrenal hormones, insulin, glucose, etc.) was obtained, although adrenocortical hyperplasia was seen. The pivotal type of study needed to test the proposed mechanism, i.e. determining if interfering with the mechanism prevents the tumor increase, was not performed.

Even if prolactin as a mechanism is accepted, there is no evidence that it would not be operative in humans (again, with the possible exception of mammary tumors. Most [all ?] dopamine-blocking antipsychotic drugs produce mammary tumors in rodents but as a class are not thought to produce mammary tumors in humans [although labeling notes that some breast tumors may be prolactin-dependent]; however a more recent study [which, interestingly, included MET], suggested a possible, small increase in humans [Wang, et. al., Arch. Gen. Psychiat. 59, 1147-1154, 2002]). MET increases prolactin at therapeutic doses in humans.

The increase in tumors by MT 100 in the rat study are presumably due to MET, since no increases were seen in the NAP-alone group (although note that incidences in the high dose combo group tended to be greater than in the MET-alone group; see below). It is not clear whether the effects of MET are due to a genotoxic or epigenetic mechanism. Results of genotoxicity studies of MET are varied, although the more recent studies done by the sponsor were negative. A p53 mouse study of MT 100, MET, and NAP was negative, although the doses of MET could have been pushed somewhat higher, and the sensitivity of the p53 assay has been called into question. Assuming a non-genotoxic mechanism, there is somewhat of a safety margin with respect to expected human plasma levels (except for female mammary tumors, where there was no clear NOEL established); however note that if prolactin is indeed the cause of the tumors, its levels are increased by therapeutic doses of MET. On the other hand, the proposed human administration will be intermittent, which lowers the risk for a non-genotoxic carcinogen. Also, these results should be viewed in the context of other drugs used in migraine, several of which have carcinogenicity findings described in the labeling as indicated in Dr. Haberny's review. (As noted above, several antipsychotic drugs also have carcinogenicity findings, although this is generally considered to be a more serious indication).

(It is noted that the incidences of several of the above tumors tended to be greater in the high dose combo group than in the group treated with MET alone at the same dose as given in combination. These differences were not statistically significant, but as noted by the statistical reviewer the study was not well-powered to detect differences between these two groups, and in most cases the value in the MET-alone group did not achieve statistical significance compared to control. Mean plasma MET levels [AUC] were about 15-25% greater [not clear if statistically significant] when given with NAP; it is not known if this difference could account for the tumor differences. Plasma prolactin levels were not clearly different between the two groups).

A full reproductive toxicity battery was performed with MT 100. The need for these studies was primarily driven by the lack of adequate studies for NAP (EOP 2 meeting 3/31/99). The studies performed here adequately evaluated NAP (there was a signal for a teratological effect in rabbit; see Dr. Haberny's review); however since the clinical ratio was used, the doses of MET were extremely small (plasma levels were generally not detectable), and thus any potential interaction was not adequately evaluated. In light of the fact that the use of the clinical ratio for animal studies is generally accepted, and in fact was previously agreed to for studies with MT 100 (pre NDA meeting of 2/27/00), and that pronounced interactions were not seen in other studies using adequate (see below) doses of NAP and

MET, it is not felt necessary to repeat these studies. However, I would make a plea for future animal studies of any drug combination not to default to use of the clinical ratio. In the present case, use of the clinical ratio led to a miniscule dose of MET because NAP (as with other drugs of this class) is very poorly tolerated in animals. A more rational approach would be to use a ratio based on the sensitivity of the test species to the individual components, e.g. the ratio of the MTD values of the individual components (as was done for the carcinogenicity studies for MT 100).

*Note that, as indicated in Dr. Haberny's review, the exec CAC did not consider there to be a clear drug effect on pancreatic tumors since although the increased incidence of carcinomas was statistically significant, the incidence of adenomas and carcinomas combined was not. I strongly disagree with this reasoning; we routinely consider tumor nature/severity/progression in our evaluations of carcinogenicity. In fact, this position is clearly advocated in the primary document we use to make decisions about combining tumors, i.e. McConnell, et. al., JNCI 76: No. 2, 1986, p. 283-289 (esp. p. 285).

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Barry Rosloff
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PHARMACOLOGIST