

## POZEN TARDIVE DYSKINESIA (TD) ADVISORY GROUP

### CONSENSUS STATEMENT REGARDING RISK OF TD WITH USE OF MT 100 FOR ACUTE TREATMENT OF MIGRAINE

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## CONSENSUS STATEMENT

The Advisory Group reached consensus that the risk of tardive dyskinesia (TD) with MT 100 use in the episodic, single dose acute treatment of migraine is quite small [and should not approximate a risk of 1%]. The risk present can be mitigated and managed through incorporation of the suggested limitations on use, and clear guidance on discontinuation of treatment if there is any evidence of acute dystonia, TD, or any other movement disorder.

## BACKGROUND

POZEN convened this Advisory Group in conjunction with the 9<sup>th</sup> International Congress of Parkinson's Disease & Movement Disorders held in New Orleans, LA on March 6, 2005 in order to more fully assess any potential risk of TD associated with the use of MT 100 for the acute treatment of migraine. All members of the Advisory Group have extensive clinical experience in the assessment and/or management of patients who have exhibited TD and all had been provided with the following information: data describing results of the MT 100 clinical development program for migraine, including the studies leading to choice of dose of metoclopramide hydrochloride for inclusion in MT 100 Tablet (16mg; 13.5 mg metoclopramide base); Phase III efficacy data showing the effects of MT 100 versus naproxen sodium in acute treatment of migraine, including efficacy as assessed by sum of pain intensity differences (SPID) analyses; Phase III safety data, including adverse events reported from POZEN Study MT100-302 enrolling 1006 patients eligible for treatment of multiple episodes of migraine for up to one year; and data summarized from the literature and from regulatory adverse event registries (FDA and MHRA) providing information describing cases of tardive dyskinesia from post-marketing experience with metoclopramide formulations. The Advisory Group members were aware that the FDA did not conclude that MT 100 is an effective migraine agent and were shown the statement related to risk of TD from the not approvable letter (NAL).

The Advisory Group was also provided with the FDA-approved labeling for Reglan® (metoclopramide) and a recent publication describing cases of TD reported to the FDA AERS system (Shaffer 2004) that summarized details of 87 cases reported up to 2003 that implicated metoclopramide as causal for TD.

## RISK OF ACUTE DYSTONIA WITH USE OF MT 100

The POZEN MT100-302 study was a one year safety study. Of the 1006 patients enrolled, 621 completed six months and 329 of these patients completed 12 months of the study. Overall, patients in this study treated 23,195 migraine attacks with single doses of MT100. Forty-six percent of patients took more than 24 doses of MT 100. The current Prescribing Information for Reglan® identifies the incidence of acute dystonic reactions as approximately 0.2%. The Advisory Group members noted that the POZEN MT100-302 study had enrolled 1006 patients and that one patient experienced several events described as acute dystonia as he continued to use MT 100 for migraine attacks; thus, in this prospective study, the frequency of acute dystonia was 1/1006 patients or 0.1%. Dr. Schapira noted that this study was the only prospectively conducted study to determine the incidence of events with repeated episodic use of metoclopramide (as contained in MT 100). Dr. Friedman noted that in POZEN study MT100-302, an objective measurement to

assess movement disorders (i.e. AIMS) was not used. The Advisory Group was also aware that in another POZEN Phase III study, one female patient had experienced one episode of acute dystonia after (blinded) use of MT 100.

Consensus was reached that patients who experience acute dystonic reactions with metoclopramide use appear to be at increased risk of more serious events, including drug-induced parkinsonism and TD with further use of this drug, although there is no published epidemiological data to support this conclusion. The Advisory Group members agreed that any patients who experience acute dystonic reactions, or any other acute movement disorder that is linked to use of MT 100, should not be retreated (i.e. rechallenged) with MT 100 or any form of metoclopramide. The members noted that the current Reglan® Prescribing Information does not contain this information.

Consensus was reached that the risk of TD should be relatively lower in the migraine patient population that, although predominantly female, would generally not have advanced age as a risk factor, would use a relatively low dose of metoclopramide on an episodic, single dose basis for treatment of single attacks of migraine, and would not have continuous daily exposure to the drug. The Advisory Group believed that the risk of TD with use of MT 100 should be much lower than the risk of TD in patients treated for psychotic disorders. This is because the dose of metoclopramide in MT 100 is substantially lower than corresponding doses of antipsychotic drugs, and total duration of exposure will be much lower with episodic, single dose treatment.

#### RISK FACTORS FOR OCCURRENCE OF TD WITH USE OF MT 100

The Advisory Group noted that no TD events had been reported in the entire MT 100 clinical development program, including Study MT100-302.

The Advisory Group discussed the diagnostic difficulty in recognition of TD and agreed that there is a spectrum of movement disorders that may be appropriately or inappropriately labeled as TD. Dr. Kapur said that TD involving truncal musculature might be harder to recognize than TD affecting facial muscles. Dr Schapira noted that in a case-control study in a VA patient population, 17% of controls that had not received metoclopramide were said to have TD (Ganzini 1993).

The Advisory Group members agreed that metoclopramide, as a dopamine receptor antagonist, was one of the currently marketed drugs most commonly associated with TD, a hyperkinetic movement disorder and a well-established iatrogenic condition, but that certain risk factors for the occurrence of TD could be identified. Dr. Jankovic and his colleagues had recently reviewed the drugs implicated in causation of TD among 116 patients evaluated in the Movement Disorders Clinic at Baylor College of Medicine (Presented at the 9<sup>th</sup> International Congress of Parkinson's Disease & Movement Disorders held in New Orleans, LA on March 6, 2005). They reported that the most common medications associated with the onset of TD were metoclopramide (26% of cases), haloperidol (10% of cases), and risperidone (8% of cases). Among these cases, patients with TD were most often female (83%) with a mean age of TD onset of 58.6 (+/- 14.1) years.

A recent publication (Shaffer 2004) summarized details of 87 cases of TD reported to the FDA AERS system up to 2003 that implicated metoclopramide as causal for TD. In this FDA database, 67% of cases occurred in females with a mean age of 60 (+/- 22) years. The mean daily dose of metoclopramide used was 33 mg (+/- 14mg) per day and the duration of treatment before report of TD was a mean of 753 (+/- 951) days.

The Advisory Group discussed and confirmed that the generally agreed risk factors for TD in patients using dopamine receptor antagonists include: advanced age (e.g. 60 years or above), female gender, presence of diabetes, presence of concurrent affective disorder(s), and less well characterized factors that relate to dose and duration of treatment. The members noted that the current Reglan® Prescribing Information adequately described the increased risk of TD in elderly women.

The members noted that the majority of the use of metoclopramide in the United States is for the treatment of gastrointestinal conditions including GERD and diabetic gastroparesis. Dr. Kapur said that it was not clear if there was a dose of metoclopramide that did not carry some risk of TD. Dr. Jankovic noted that nearly all cases of metoclopramide-associated TD that he has seen during his career have been associated with continuous daily use of the drug and that he knows of no evidence that episodic, single dose use of metoclopramide would cause TD.

#### RISK OF IRREVERSIBLE TARDIVE DYSKINESIA WITH USE OF MT 100

The Advisory Group agreed that elderly patients appear to be at increased risk for irreversibility of TD and the prospect for complete reversibility of TD is greatest with early detection and prompt discontinuation of the dopamine receptor antagonist. Dr. Kapur noted that patients treated for schizophrenia might develop TD while continuing to take antipsychotic medication that masks TD symptoms, thus delaying detection of the movement disorder. Unlike the common clinical situation in patients with psychotic disorders, if a movement disorder were to develop in a patient with migraine, permanent discontinuation of MT 100 would not be problematic for continued medical management of migraine. In addition, patients with migraine are a population that, compared to patients with psychotic disorders, would be more likely to self-report acute movement disorders and/or early signs of TD, resulting in medical consultation and early discontinuation of MT 100 treatment.

The Advisory Group reached consensus that if TD were to occur in a patient with migraine who used MT 100 for episodic, single dose acute treatment, it is likely that the TD would be reversible because the patient would be relatively young, would not have other CNS disease, would not have had the TD symptoms for very long, and would be able to discontinue use of metoclopramide immediately.

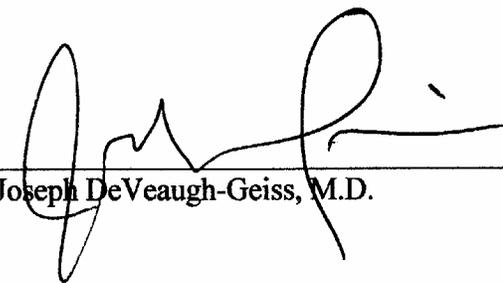
## RECOMMENDATIONS FOR PRESCRIBING LIMITATIONS

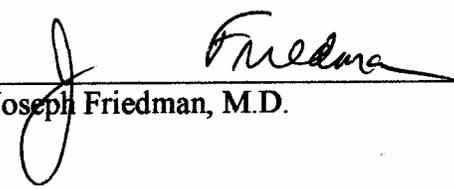
The Advisory Group discussed the types of patients for whom the use of MT 100 should be contraindicated and/or cautioned. A consensus was reached that MT 100 should be contraindicated in patients with episodic or persistent dystonia or other involuntary movement disorder, in patients with Parkinson's disease, and in patients using any dopamine receptor antagonist for any other indication. It was also recommended that MT 100 should not be used in patients less than 18 years of age or older than 65 years of age and those patients who would not be compliant with periodic evaluation for any evidence of drug-induced movement disorder.

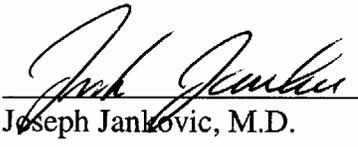
## REFERENCES

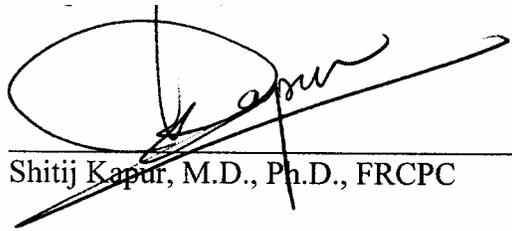
1. Ganzini L, Casey DE, Hoffman WF, McCall A.L. (1993): The Prevalence of Metoclopramide-Induced Tardive Dyskinesia and Acute Extrapyrmidal Movement Disorders. *Arch Intern Med* 153: 1469-1475.
2. Shaffer D, Butterfield M, Pamer C, Macey AC (2004): Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride. *J Am Pharm Assoc* 44: 661-665.

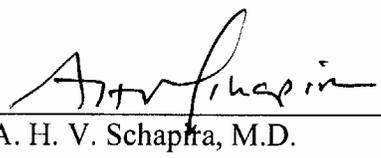
For the TD Advisory Group

  
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