

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 5, 2005

FROM: Mary Ross Southworth, PharmD, Safety Evaluator
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THROUGH: Mark Avigan, M.D., C.M., Director
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TO: Russell Katz, M.D., Director
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SUBJECT: ODS Postmarketing Safety Review
Drug(s): Myzan (MT 100; naproxen/metoclopramide)
Sponsor: Pozen
NDA: 21-645
Event: Tardive dyskinesia, parkinsonism, akathisia, acute dystonia,
neuroleptic malignant syndrome

PID #: D050036

EXECUTIVE SUMMARY

The Division of Neuropharmacologic Drug Products requested an AERS review of cases of movement disorders and neuroleptic malignant syndrome relating to metoclopramide use. Myzan (formerly MT 100) a combination of naproxen sodium (500 mg) and metoclopramide (16 mg), is being considered for approval for the indication of acute treatment of migraine (intermittent dosing). To characterize these possible movement disorders related to metoclopramide use, AERS cases that were coded with the following movement disorders were retrieved and analyzed: tardive dyskinesia, metoclopramide-induced Parkinsonism, akathisia, and acute dystonia. A total of 401 cases were included in the analysis.

The characteristics of the 401 cases retrieved from the AERS database involving movement disorders and NMS related to metoclopramide use reinforce what has been shown in the literature and product labeling regarding these adverse events. For the most part, the movement disorders are reversible over time. Unfortunately, some patients continue to have symptoms or recover with sequelae after the drug has been discontinued; most of these cases are associated with chronic (>30 days) therapy with metoclopramide.

When considering this new indication of metoclopramide (treatment of acute migraine), in which the nature of the drug regimen is intermittent and not chronic, it is important to ensure that this type of therapy possesses a favorable risk/benefit ratio; an excess risk of irreversible movement disorder and NMS would be unacceptable. There is a dearth of data in AERS specifically involving adverse events related to intermittent use of metoclopramide, however the following information is relevant:

- Most of the adverse events where the symptoms were continuing at the time of reporting involved chronic therapy (>30 days of continuous use-with the exception of acute dystonia)
- There were few (8) cases involving adult patients in which short term therapy (≤ 3 days) led to continuing symptoms: 1 Parkinsonism, 2 tardive dyskinesias, no akathisia cases, 4 acute dystonia, and 1 NMS. Most of these cases involved 3 or more doses before the adverse event occurred. In only one of these cases did the reaction occur after one dose and no information was provided regarding dose or route of administration (ISR 1584424). In another case where the reaction occurred after 2 doses of 20 mg oral metoclopramide, the dystonia resolved with diphenhydramine. The continuing symptoms were left sided weakness and temporary loosening of the teeth, not symptoms consistent with dystonia.
- There were 15 deaths in the case series.
 - The duration of metoclopramide therapy before death occurred ranged from 1 dose to 8 months
 - In the majority of these cases the patient had a concomitant disease (cancer, sepsis) that could have contributed to the death.
 - In many of the cases the patient was on concomitant medications (haloperidol, cyclobenzaprine) which could have contributed to the adverse event
- There were 5 patients who experienced suicidal ideation
 - The duration of metoclopramide therapy before suicidal ideation occurred ranged from 3 doses to 5 months
 - One patient was on a concomitant antidepressant
- There were 2 suicides
 - The duration of metoclopramide therapy before suicide ranged from 2 to 4 months

The characteristics of the movement disorders and NMS related to metoclopramide use observed in the cases from the AERS database correlate well with what has been reported in the literature. There were no cases in AERS which presented movement disorders (reversible or otherwise) or NMS with intermittent, short term use of metoclopramide. It is unknown whether this is because this dosing regimen typically does not occur, or, if it does, very few adverse events have occurred (or been reported) because of it.

Data on irreversible movement disorders and NMS relating to short term use (≤ 3 days) of metoclopramide reveals only a small number of cases. In addition, there are relatively few deaths/suicides attributed to metoclopramide alone and in most of these cases, the patient had concomitant diseases or medications which could have contributed to the outcome.

In conclusion, we do not believe the safety data from the AERS database preclude the proposed occasional use of metoclopramide for the treatment of acute migraine. According to data in the AERS cases, the occurrence of irreversible movement disorders and NMS is largely a risk associated with chronic use of metoclopramide. From information that has been provided in the AERS reports it is not possible to differentiate risk associated with chronic (frequent) intermittent treatment compared to chronic continuous treatment. A separate concern that has been raised by this analysis is the potential for drug – drug interactions that enhance the likelihood of acute dystonic reactions, even after short-term use.

The Division of Surveillance, Research and Communications Support will submit a separate consult on patterns of metoclopramide use in the US as well as duration of therapy.

INTRODUCTION

The Division of Neuropharmacologic Drug Products requested an AERS review of cases of movement disorders and neuroleptic malignant syndrome relating to metoclopramide use. Myzan (formerly MT 100) a combination of naproxen sodium (500 mg) and metoclopramide (16 mg), is being considered for approval for the indication of acute treatment of migraine. Metoclopramide is known to cause movement disorders particularly with prolonged use which, in some cases, may continue after the drug has been discontinued (see Current Labeling and Movement Disorders below).

When used for migraine treatment, the use of Myzan would be chronic, but intermittent (i.e., episodic based on occurrence of migraine symptoms- one dose per migraine, up to 6 times per month; the use of a second tablet during a single migraine is not recommended in the proposed dosing regimen). It is unknown what the risk related to movement disorder is when metoclopramide is used in this manner. To characterize these reactions, AERS cases of metoclopramide that were coded with the following movement disorders were analyzed: tardive dyskinesia, metoclopramide-induced Parkinsonism, akathisia, and acute dystonia. Information regarding the following is provided:

- Number of case reports (domestic vs. foreign) since marketing
- Description of the daily dose of metoclopramide prior to the reaction
- Description of the duration of treatment
- Identification of associated risk factors
- Reversibility

In addition, metoclopramide is also associated with a risk of neuroleptic malignant syndrome (NMS). Similar information was requested in order to characterize incidence of NMS related to metoclopramide use.

CURRENT LABELING¹

Metoclopramide is currently available in injection form (approved 1979) and tablet form (approved 1980). Metoclopramide tablets are indicated for symptomatic gastroesophageal reflux and for diabetic gastroparesis. The recommended dose is 5 to 20 mg four times daily; the labeling indicates that duration of therapy should not exceed 12 weeks. Metoclopramide is contraindicated in patients receiving other drugs likely to cause an extrapyramidal reaction. There are no drug-drug interactions listed in the labeling which would have an impact on co-administration of naproxen or worsening of adverse reactions related to movement disorders.

The label also states that the absolute bioavailability of oral metoclopramide is about 80% that of intravenous metoclopramide. The time to peak serum concentration is shorter with the IV formulation, as well. These pharmacokinetic differences in dosage forms may have an impact on the characteristics of cases involving movement disorders associated with oral vs. IV administration of metoclopramide.

The Warning section contains the following information regarding metoclopramide-induced movement disorders and NMS. Extrapyramidal symptoms occur in approximately 1 out of 500 patients receiving daily dosages of 30 to 40 mg. Parkinsonian-like symptoms may occur after prolonged use and generally subside within 2 to 3 months of discontinuation. Tardive dyskinesia (TD) also occurs, generally being more common with longer duration of treatment. However, it may also occur with shorter durations of treatment with lower doses. NMS has been rarely reported with metoclopramide use.

Notably, metoclopramide has been used clinically for a variety of non FDA approved uses including: ileus, adjunctive analgesia, prevention of chemotherapy induced nausea and vomiting, hiccups, and migraine headache.

MOVEMENT DISORDERS RELATED TO METOCLOPRAMIDE USE^{2,3,4,5}

Metoclopramide, a dopamine antagonist, has been associated with movement disorders such as dyskinesia, akathisia, parkinsonism, chorea, myoclonus, tics and dystonia. For the purposes of this consult, focus will be placed on 4 specific movement disorders.

¹ Reglan tablets package insert (Schwarz Pharma) 2/04

² Miller LG, Jankovic JJ Metoclopramide-induced movement disorders: clinical findings with a review of the literature. Arch Intern Med 1989; 149: 2486-92.

³ Jiminez-Jimenez FJ, Garcia-Ruiz PF, Molina JA. Drug induced movement disorders. Drug Safety 1997; 16: 180-204.

⁴ DSM-IV 2000.

⁵ Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Intern Med 1993; 153: 1469-1475

Tardive dyskinesia (TD) is characterized by persistent, abnormal involuntary movements (commonly seen in the face and mouth area) and choreic movements of the trunk. This term may also be used to describe other movement disorders such as tremor, dystonia, myoclonus, and *akathisia*. For drug-induced TD, the typical duration of exposure is generally considered to be >30 days. Although often thought of as a chronic disease, about 1/3 of patients will recover in about 3 months; about half will recover in 12 to 18 months⁴. Proposed risk factors include: advanced age, female gender, prolonged exposure to or high dose of antipsychotic drugs, prior existence of movement disorders, diabetes, organic brain dysfunction, brain atrophy, affective disorders, schizophrenia, family history of mental illness, alcohol abuse and diabetes. Drugs that have been associated with the development of TD include: antipsychotics, metoclopramide, calcium channel blockers, antidepressants, lithium, and anxiolytics.

Drug-induced parkinsonism is characterized by resting tremor (typically postural and symmetrical), cogwheel rigidity, and akinesia. These symptoms often are accompanied by other movement disorders such as *TD* and *akathisia*. Parkinsonism may not necessarily abate with discontinuation of the offending drug. Risk factors include: long duration of therapy and schizophrenia. Agents associated with drug induced parkinsonism include: antipsychotics, calcium channel blockers, benzamides (metoclopramide, cisapride, domperidone), antiemetics, antidepressants, lithium, diazepam, and anticonvulsants.

Akathisia is characterized by a feeling of restlessness and a need for constant movement or inability to sit still (rocking, pacing, toe tapping, face rubbing). Risk factors have not been elucidated; suggested factors include: drug dosage and potency. Drugs that have been associated with development of akathisia include: antipsychotics, metoclopramide, reserpine, levodopa, antidepressants, calcium channel blockers, lithium, anxiolytics, and anticonvulsants.

Acute dystonia is characterized by sustained muscle contractions with twisting, pulling, and abnormal postures which occur within minutes to hours of drug initiation. Risk factors for the development include: young age and male gender. Other drugs associated with the development of dystonia include antipsychotics, cisapride, antidepressants, anticonvulsants, and calcium channel blockers.

A patient may exhibit more than one type of drug induced movement disorder as is seen in some of the cases presented below.

Treatment to reverse drug induced movement disorders largely consists of anticholinergic agents (e.g., diphenhydramine, benztropine). Other agents used include muscle relaxants and anxiolytics.

NEUROLEPTIC MALIGNANT SYNDROME^{6,7}

⁶ Bhanushali MJ, Tuite PG. The evaluation and management of patients with neuroleptic malignant syndrome. *Neurol Clin N Am* 2004; 22: 389-411.

NMS is a rare, but potentially fatal reaction associated with neuroleptic use. This reaction has also been reported with metoclopramide use. Characteristics include fever, muscle rigidity, autonomic dysfunction, and decreased consciousness. Risk factors for developing NMS include high doses of neuroleptics, psychiatric conditions, organic brain abnormalities, young age, and male gender. Duration of treatment seems to have no impact on the development of NMS. Drugs that have been associated with development of NMS include: neuroleptics, atypical antipsychotics, metoclopramide, antiemetics, amphetamines, lithium, and antidepressant overdose.

SEARCH STRATEGY/RESULTS

A search of the FDA’s Adverse Event Reporting System (AERS) database on January 18, 2005 was conducted to capture reports of all adverse events associated with the use of metoclopramide. A total of 3418 crude reports were contained in AERS; the top 8 Preferred Terms (PT) for metoclopramide were Extrapyramidal Disorder (365), Dystonia (257), Depression (248), Tremor (227), Anxiety (152), Dyspnea (134), Vomiting (134), and Nervousness (120). There were 928 total crude reports for the High Level Term (HLT) Dyskinesias and Movement Disorders. The top 6 PT terms for this HLT were Extrapyramidal Disorder (365), Dystonia (257), Tardive dyskinesia (110), Dyskinesia (99), Tremor (98), and Akathisia (67). The PT’s are not mutually exclusive in that a report may be coded with more than one PT.

A search with metoclopramide and each of the events of interest was performed. The following table shows the number of crude reports for each MEDDRA term.

Table 1. Crude Reports

MEDDRA term	Number of crude reports
Parkinson’s disease and Parkinsonism (HLT)	48
Tardive dyskinesia (PT)	110
Akathisia (PT)	67
Dystonia (PT)	257
Neuroleptic malignant syndrome (PT)	45

The cases were then reviewed to assess their appropriateness for inclusion into the case series. Cases were excluded for the following reasons: duplicate cases, cases involving drug overdose, inappropriate MEDDRA term applied to the case, and adverse event occurred after withdrawal of long term therapy.

For organizational clarity, cases were classified based on the diagnosis stated in the actual AERS case report. Therefore, in some cases, the outcome may not be consistent with the

⁷ Nierenberg D, Disch M, Manheimer E. Facilitating prompt diagnosis and treatment of the neuroleptic malignant syndrome. Clin Pharmacol Ther 1991; 50: 580-6.

movement disorder classification (i.e., cases of tardive dyskinesia where the symptoms were resolved; acute dystonia cases where the symptoms were continuing). In addition, the duration of therapy listed for each movement disorder is extracted directly from each case, and virtually all cases made no distinction between chronic intermittent and chronic continuous therapy; therefore no conclusion can be made regarding the continuity of therapy throughout the therapy period.

Parkinsonism

A total of 35 unique cases were included in the review for metoclopramide associated Parkinsonism. In general, the occurrence of Parkinsonism associated with metoclopramide use is in an older population (mean age 60.5 years) and is associated with chronic treatment (mean duration of treatment 115 days). The range of doses in the case series was 10 to 80 mg daily with a mean of 36.6 mg (generally within the recommended dosing range of 20 to 80 mg per day). The most common indications were gastro-esophageal reflux (9), gastroparesis (7), and nausea/vomiting (6). Frequent concomitant medications included antidepressants (5 cases) and antipsychotics (3 cases). Concomitant medical conditions included diabetes (8 cases) and renal failure (2 cases). The majority of cases (15 cases) reported that symptoms improved or resolved after discontinuation of metoclopramide (time course to resolution was often not reported), both with and without treatment of the adverse event. In 8 cases symptoms were noted as continuing at the time of reporting.

This table summarizes the findings for the Parkinsonism cases. Further discussion of the cases (including death cases) is found below under **Summary of Cases.**

Table 2. Demographics and Clinical Characteristics of Parkinsonism associated with metoclopramide use.

Age	Range Mean±SD Unreported	18 to 88 years 60.5 ± 20.6 years 2
Gender	Male Female Unreported	13 21 1
Source	Foreign Domestic	3 (Puerto Rico, Germany, UK) 32
Daily dose	Range Mean ±SD Unreported	10 to 80 mg 36.6 ± 16.9 mg 10
Route	IV PO Unreported	2 24 9
Duration	Range	1 dose to 1460 days

	Median Mean Unreported	60 days 115 days 10
Indication	Gastroparesis GERD Nausea/Vomiting Hernia Other GI disorder Not Reported	7 9 6 1 3 9
Outcome	Death Disability Hospitalization/ED Life threatening Not serious/Not reported	2 5 17 1 10
Suspected Concomitant Medications [†] (# of cases)	Antidepressant Antipsychotic Pain medication Other None/None reported	5 3 1 4 24
Suspected Concomitant Medical Conditions ^Δ (# of cases)	Tremor Schizophrenia Bipolar Parkinson's disease Diabetes Renal failure None/None Reported	1 1 1 1 8 2 24
Treatment of Adverse Event*	Diphenhydramine/Anticholinergic Amantadine Benztropine Anxiolytic Antiparkinson medication Other	4 2 3 2 6 2
Recovery [‡] (# of cases)	Symptoms decreased/ improved Recovered Symptoms continuing Not reported Suicide Death	7 8 8 10 1 1
Concomitant Movement disorders (# of cases)	Tardive dyskinesia Dystonia Other	5 1 1

[†]These medications are associated with Parkinson's-like symptoms or are a risk factor for developing Parkinsonism. "Other" includes loperamide, cisapride, donepezil, tramadol, midodrine, cimetidine. Multiple drugs could be listed in one case.

Δ These conditions may be considered risk factors for developing movement disorders

*A case could have more than one treatment. Not all cases reported a treatment.

‡ Status of recovery at the time of reporting (with or without treatment). In all cases, metoclopramide was discontinued with occurrence of the adverse event.

Tardive Dyskinesia

A total of 68 unique cases were included in the review for metoclopramide associated TD. In general, the occurrence of tardive dyskinesia associated with metoclopramide use is in an older population (mean age 57.2 years) and is associated with chronic treatment (mean duration of treatment 638 days). The range of doses in the case series was 5 to 80 mg daily with a mean of 35 mg (within the recommended dosing of 20 to 80 mg daily). The most common indications were gastro-esophageal reflux (16) and gastroparesis (11). Frequent concomitant medications included antidepressants (14 cases), calcium channel blockers (6 cases) and antipsychotics (4 cases). A common coexisting medical condition was diabetes (9 cases). The majority of cases reported that symptoms continued at the time of reporting (20 cases). In 12 cases symptoms were reported as improved or resolved after discontinuation of metoclopramide (time course to resolution was often not reported), both with and without treatment of the adverse event.

This table summarizes the findings for the tardive dyskinesia cases. Further discussion of the cases (including death cases) is found below under **Summary of Cases**

Table 3. Demographics and Clinical Characteristics of Tardive Dyskinesia associated with metoclopramide use.

Age	Range Mean±SD Unreported	14 to 90 years 57.2 ± 18.3 21
Gender	Male Female Unreported	20 38 10
Source	Foreign Domestic	2 (New Zealand, Australia) 66
Daily dose	Range Mean ±SD Unreported PRN dosing	5 to 80 mg 35 ± 14.3 mg 27 3
Route	IV: PO: Both Unreported	4 52 1 11
Duration	Range	1 to 4715 days

	Median Mean Interquartile Range Unreported	180 days 638 days 29.5, 821.25 days 20
Indication	Gastroparesis GERD Nausea/Vomiting Hernia Other GI disorder Not Reported	11 16 7 3 5 26
Outcome	Required intervention Disability Hospitalization/ED Life threatening Not serious/Not reported	2 17 11 1 37
Suspected Concomitant Medications [†] (# of cases)	Antidepressant Antiemetic Antipsychotic Lithium Calcium channel blocker Other None/None reported	14 3 4 1 6 2 43
Suspected Concomitant Medical Conditions ^Δ (# of cases)	Movement disorder on other tx Schizophrenia Bipolar Tardive Dyskinesia Brain abnormality [°] Diabetes Renal insufficiency/failure None/None Reported	1 2 1 2 2 9 2 54
Treatment of Adverse Event [*]	Diphenhydramine/Anticholinergic Benzotropine Anxiolytic Tetrabenazine Amantadine Antidepressant Baclofen Other	10 10 10 4 1 3 3 11
Recovery [‡] (# of cases)	Symptoms decreased/ improved Recovered Symptoms continuing Suicidal thoughts Not reported	8 4 20 2 34
Concomitant Movement	Akathisia Dystonia	5 8

disorders (# of cases)	Parkinson's/tremors	10
	Other	3

†These medications are associated with TD or are a risk factor for developing TD. “Other” includes methylphenidate, zolpidem. Multiple drugs could be listed in one case.

Δ These conditions may be considered risk factors for developing movement disorders

°s/p hemispherectomy in one patient, cancer with metastasis to brain in one patient

*A case could have more than one treatment. Not all cases reported a treatment.

‡ Status of recovery at the time of reporting. In all cases, metoclopramide was discontinued after the adverse event occurred.

Akathisia

A total of 57 unique cases were included in the review for metoclopramide associated akathisia. In general, the occurrence of akathisia associated with metoclopramide use is in a middle aged population (mean age 45.7 years) and is associated with chronic treatment (mean duration of treatment 245 days). The range of doses in the case series was 5 to 200 mg daily with a mean of 42.3 mg. In two cases, the dose exceeded the recommended maximum daily dose of 80 mg. The most common indications were nausea/vomiting (15) and gastroesophageal reflux (13). Frequent concomitant medications included antidepressants (7 cases), antiemetics (6 cases) and antipsychotics (6 cases). There were no common coexisting medical conditions, although brain and muscular disorders, diabetes, and preexisting dyskinesias were reported. The majority of cases reported that symptoms improved or resolved after discontinuation (time course to resolution was often not reported), both with and without treatment (31 cases). In 9 cases symptoms were reported as continuing at the time of reporting.

This table summarizes the findings for the akathisia cases. Further discussion of the cases (including death cases) is found below under **Summary of Cases**

Table 4. Demographics and Clinical Characteristics of Akathisia associated with metoclopramide use.

Age	Range	0.2 to 94 years
	Mean±SD	45.7 ± 18.7
	Unreported	8
Gender	Male	19
	Female	34
	Unreported	4
Source	Foreign	4 (UK-3, Germany)
	Domestic	53
Daily dose	Range	5 to 200 mg
	Mean ±SD	42.3 ± 35.2 mg
	Unreported	10
	PRN dosing	2
	Weight based	1

Route	IV PO SQ IV/PO Unreported	11 42 1 1 2
Duration	Range Median Mean ± SD Interquartile range Unreported	1 to 2555 days 17 days 245 days 2, 86.25 days 20
Indication	Gastroparesis GERD Nausea/Vomiting Hernia Chemotherapy pretx Ulcer Other GI disorder Other Not Reported	7 13 15 1 3 2 8 3 5
Outcome	Disability Hospitalization/ED Death Not serious/Not reported	3 20 1 33
Suspected Concomitant Medications [†] (# of cases)	Antidepressant Antiemetic Antipsychotic Phenytoin Calcium channel blocker Other None/None reported	7 6 6 3 4 10
Suspected Concomitant Medical Conditions ^Δ (# of cases)	Muscular disorder Dystonia/akathisia/tremor Organic brain disorder Diabetes Psychologic issues None/None Reported	2 3 2 3 2 46
Treatment of Adverse Event [*]	Diphenhydramine/Anticholinergic Benzotropine Anxiolytic Tetrabenazine Propranolol Botulism Toxin Antidepressant Other	16 8 14 1 3 2 3 11
Recovery [‡]	Symptoms decreased/ improved	11

(# of cases)	Recovered	20
	Symptoms continuing	9
	Suicidal thoughts	1
	Not reported	16
Concomitant Movement disorders (# of cases)	Tardive dyskinesia	8
	Dystonia	1
	Parkinson's/tremors	9
	Other	4

†These medications are associated with movement disorders or are a risk factor for developing movement disorders. “Other” includes phenobarbital, cisapride, acyclovir, ciprofloxacin, clonazepam, midazolam, domperidone, estazolam, tramadol. Multiple drugs could be listed in one case.

Δ These conditions may be considered risk factors for developing movement disorders.

*A case could have more than one treatment. Not all cases reported a treatment.

‡ Status of recovery at the time of reporting. In all cases, but one, metoclopramide was discontinued after the adverse event occurred. In the one case, symptoms resolved despite continued metoclopramide therapy

Acute Dystonia

A total of 203 unique cases were included in the review for metoclopramide associated dystonia. In general, the occurrence of acute dystonia associated with metoclopramide use is in a younger population (mean age 32.3 years) and is frequently associated with initial dosing and higher doses (median treatment duration 2 days; mean duration of treatment 49.7 days). The range of doses in the case series was 0.6 to 800 mg daily with a mean of 71.4 mg. In 25 cases, the dose exceeded the recommended maximum daily dose. The most common indications were nausea/vomiting (57), pre-treatment for chemotherapy (29), and gastro-esophageal reflux (26). Frequent concomitant medications included antidepressants (16 cases) and antiemetics (22 cases). Concomitant medical conditions included diabetes (9 cases); history of movement disorder with another medication (6 cases) and renal disease (4 cases). The majority of cases reported that symptoms improved or resolved (115 cases) after discontinuation of metoclopramide (time course to resolution was often not reported), both with and without treatment. In 12 cases symptoms were reported as continuing at the time of reporting.

This table summarizes the findings for these cases. Further discussion of the cases (including death cases) is found below under **Summary of Cases**

Table 5 Demographics and Clinical Characteristics of Acute Dystonia associated with metoclopramide use.

Age	Range	0.1 to 84 years
	Mean±SD	32.3 ± 21.5 years
	Unreported	26
Gender	Male	79
	Female	115
	Unreported	10
Source	Foreign	18 (Denmark, UK [4], Taiwan, Spain [3],

		Italy [2], South Africa, France, Australia [4], Belgium)
	Domestic	185
Daily dose	Range Mean \pm SD Various dosing PRN Unreported	0.6 to 800 mg 71.4 \pm 136.2 mg 1 5 42
Route	IV: PO: IV/PO: IM: IM/PO PR Unreported	68 113 5 2 1 1 12
Duration	Range Median Mean Interquartile range Unreported	1 dose to 2065 days 2 days 49.7 days 1, 2 days 34 days
Indication	Gastroparesis GERD Nausea/Vomiting Hernia Chemotherapy pretx Ulcer Pre-operative Other GI disorder Other Not Reported	13 26 57 6 29 4 7 21 4 36
Outcome	Death Disability Hospitalization/ED Life threatening Required intervention Not serious/Not reported	6 3 60 5 4 125
Suspected Concomitant Medications [†] (# of cases)	Antidepressant Antipsychotic Antiemetic Calcium Channel Blocker Other None/None reported	16 5 27 7 22 138
Suspected Concomitant	Tremor History of movement disorder	1

Medical Conditions ^Δ (# of cases)	with another medication	6
	Renal disease/failure	4
	Diabetes	9
	Other	7
	None/None Reported	182
Treatment of adverse event [*]	Diphenhydramine/Anticholinergic	90
	Benzotropine	14
	Anxiolytic	16
	Muscle relaxant	2
	Botulism Toxin	2
	Other	13
Recovery [‡] (# of cases)	Symptoms decreased/ improved	6
	Recovered	109
	Symptoms continuing	12
	Not reported	69
	Suicide/suicidal thoughts	3
	Death	5

†These medications are associated with dystonias or dyskinesias. “Other” includes cimetidine, lorazepam, domperidone, loperamide, midazolam, phenobarbital, hexamethylmelamine, and cisapride. Multiple drugs could be listed in one case.

Δ These conditions may be considered risk factors for developing movement disorders. Other includes cerebral palsy, Guillan-Barre syndrome, encephalopathy, neurological damage, organic brain injury, Parkinson’s disease, stroke

*A case could have more than one treatment. Not all cases reported a treatment.

‡ Status of recovery at the time of reporting. In all cases, but two, metoclopramide therapy was discontinued when the adverse event occurred. In those two cases the patients recovered despite continued metoclopramide therapy

Neuroleptic Malignant Syndrome

A total of 37 unique cases were included in the review for metoclopramide associated NMS. In general, the occurrence of neuroleptic malignant syndrome associated with metoclopramide use is in a middle aged population (mean age 49 years) and is not associated with chronic treatment (mean duration of treatment 18.9 days). The range of doses in the case series was 7.5 to 80 mg daily with a mean of 33.5 mg. The most common indications were gastroparesis (12) and nausea/vomiting (10). Frequent concomitant medications included antipsychotics (9 cases), antiemetics (8 cases), and antibiotics (7 cases). A common coexisting medical condition was infection (7 cases). In 11 cases the symptoms were reported as improved or recovered both with and without treatment (time course to resolution was often not reported). Eight patients died in this cases series.

This table summarizes the findings for the NMS cases. Further discussion of the cases (including death cases) is found below under **Summary of Cases**

Table 6. Demographics and Clinical Characteristics of NMS associated with metoclopramide use.

Age	Range	13 to 85 years
	Mean±SD	49.0 ± 17.7 years
	Unreported	6
Gender	Male	19
	Female	13
	Unreported	5
Source	Foreign	4 (UK, France, Switzerland, Japan)
	Domestic	33
Daily dose	Range	7.5 to 80 mg
	Mean ±SD	33.5 ± 17.0
	Unreported	8
	PRN dosing	4
Route	IV	14
	PO	7
	PR	1
	PO/IV	1
	Unreported	14
Indication	Gastroparesis	12
	Nausea/vomiting	10
	Other GI disorder	3
	Not reported	12
Duration	Range	1 to 196 days
	Median	3 days
	Mean ± SD	18.9
	Interquartile range	1, 7 days
	Unrptd/Indeterminate	16
Outcome	Hospitalization/ED	21
	Death	8
	Not reported	8
Suspected Concomitant Medications [†] (# of cases)	Antidepressant	3
	Antiemetic	8
	Antipsychotic	9
	Antibiotic	7
	Other	5
	None/None reported	14
Suspected Concomitant Medical Conditions ^Δ (# of cases)	Infection	7
	Renal disease	3
	Brain/Spinal Injury	4
	Diabetes	4
	Other	3
	None/None Reported	19
Treatment of adverse event*	Dantrolene	12
	Diphenhydramine	5

	Bromocriptine	6
	Other	10
Recovery [‡] (# of cases)	Symptoms decreased/ improved	2
	Recovered	9
	Symptoms continuing	1
	Not reported	17
	Death	8

†These medications are associated with NMS, NMS-like symptoms, or fever (infections). “Other” includes: cyclobenzaprine, cisapride, trimethobenzamide, gabapentin. Multiple drugs could be listed in one case.

Δ These conditions may be considered risk factors for developing metoclopramide toxicity, developing NMS or NMS-like symptoms. Other includes hyponatremia, advanced carcinoma, history of NMS.

*A case could have more than one treatment. Not all cases reported a treatment.

‡ Status of recovery at the time of reporting. In all cases metoclopramide was discontinued at the time of the adverse event.

CHARACTERISTICS OF CASES WITH CONTINUING SYMPTOMS

A primary concern in assessing the risk profile of Myzan, is characterizing the risk of permanent movement disorders relating to its use. Fifty cases (out of 401 total unique cases) in our review displayed continued symptoms at the time of adverse event reporting (8 Parkinsons, 20 tardive dyskinesia, 9 akathisia, 12 acute dystonia, 1 NMS-which was likely a dystonic reaction). This table does **NOT** include death cases which are summarized below. For each of these cases, the daily dose and duration of metoclopramide therapy are listed in the table below.

Table 7. Cases with Continuing Symptoms

Adverse Event	Daily Dose (mg; oral unless otherwise specified)	Duration of Metoclopramide Therapy (Days)
<i>Parkinsons</i>	NR	NR
	30	1
	NR	11
	20	60
	30	73
	40	90
	30	120
	40	203
<i>Tardive Dyskinesia</i>	NR	NR
	NR	NR
	40	NR
	NR	NR
	30	NR
	40 IV	1
	NR IV/30 mg PO	3

	40	20
	80 prn	57
	40	113
	80	135
	NR	150
	40	180
	NR	365
	5	690
	40	1095
	NR	1095
	40	1095
	40	1825
	20	4715
<i>Akathisia</i>	40	NR
	8.6 (per kg dosing)	17
	30	30
	30	37
	40	57
	30	180
	20	230
	NR	1095
	40	2555
<i>Acute Dystonia</i>	NR	NR
	NR	1
	NR	1
	10	1
	20	1
	20	2
	40	2
	NR	3
	20	77
	30	120
	40	1825
	20	2065
	<i>NMS</i>	30 prn

NR= not reported

With the exception of acute dystonia, most cases with continuing symptoms occurred in patients using the drug chronically (>30 days) which is inconsistent with the proposed use of Myzan in the treatment of acute migraine. To better characterize the risk of permanent movement disorders when using metoclopramide in a manner somewhat similar (i.e., short term use) to Myzan, additional criteria were applied and specific cases were summarized. Summaries of cases of interest are presented below.

SUMMARY OF CASES

Summaries of cases of interest for each of the movement disorders and NMS are presented below. The following criteria were necessary for inclusion of the case:

- The adverse event occurred after short term use (≤ 3 days)
- The adverse event was considered “not resolved”, “continuing”, or “resolved with sequelae” at the time of reporting
- The case involved an adult patient (≥ 18 years old)

Parkinsonism (1 case)

ISR 4173799x (US)

A 34 year old female with nausea received metoclopramide 10 mg PO TID for 3 doses and experienced difficulty breathing, extremity shaking, head and neck “jerking back” She went to the ED where she was treated with benzotropine after which she started to relax, however symptoms still occurred. She was subsequently treated with lorazepam and paroxetine, which did not completely relieve the symptoms. She was seen in the emergency room and by neurologists several times for reactions milder than the first reaction. Approximately 3 months later she still suffers from head pain, dizziness, tingling, pressure, fatigue, agitation, involuntary shaking, muscle spasms, and neck pain among other symptoms.

Tardive Dyskinesia (2 cases)

ISR 1807174 (US)

A 30 year old female received one IV dose of metoclopramide (dose unknown) followed by oral metoclopramide 10 mg TID for postoperative emesis after cholecystectomy. Concomitant therapy included ondansetron⁸ and chronic promethazine⁸. Three days later, the patient presented to the ED with complaints of severe nausea, vomiting, and diarrhea. She was treated with one dose of IV ondansetron. Subsequently, she experienced upper body tremors and spasms. Diphenhydramine and benzotropine were administered which controlled her symptoms for about 2 hours. The patient was admitted to the hospital for further treatment and the symptoms lessened, but did not resolve with continued therapy. Three days later the patients experienced severe full body tremors, blurred vision, numbness and tingling in her hands, increased facial movement, and an inability to walk. Lorazepam was prescribed to help control tremors. The tremors continued after discharge without resolution.

ISR 831120 (US)

A male (age unreported) received 4 to 5 doses of metoclopramide 40 mg IV over the course of one day. He had a past medical history of chronic renal failure, requiring dialysis. He developed tremors and was treated with benzotropine. When the benzotropine was discontinued, the tremors returned and persisted.

⁸ Labeled for extrapyramidal symptoms

Akathisia

No cases fit the inclusion criteria.

Acute Dystonia (4 cases)

ISR 1584424 (US)

A female (age unreported) received one dose of metoclopramide (dose, route unreported) and developed a dystonic reaction which was relieved by treatment with an anticholinergic agent. The patient developed blurred vision which did not resolve.

ISR 39357310 and 39316954 (US)

A 27 year old male received 3 doses of metoclopramide 10 mg PO over 2 days for diabetic gastroparesis. He also had a past medical history of diabetes. He experienced a dystonic reaction with psychotic tendencies, agitation, and agitation with suicidal tendencies on the second day of therapy. He was treated in the ED with diphenhydramine and lorazepam. Once discharged, he continued to have symptoms of inability to concentrate, slowed mental processing, difficulty focusing, eye strain, vertigo, loss of equilibrium, fatigue, dizziness, and hallucinations.

ISR 822622 (US)

A 41 year old female received 5 doses of metoclopramide 10 mg PO over 2 days for treatment of a hiatal hernia. She experienced weakness, shaking, jaw clenching shut, numbness in the jaw and cheek with difficulty speaking and numbness in her hand. She treated in the emergency room with diphenhydramine and benztropine. Several days later she was seen in her doctor's office with minimal tremors in her tongue. She was prescribed benztropine, but refused to take it. She continued to experience tingling, pulling in her cheek and drooping of the right side of her mouth at the time of reporting.

ISR 330934 (US)

A 49 year old female received 2 doses of metoclopramide 20 mg PO over 2 days for treatment of gastric reflux. Concomitant therapy included cimetidine. On day 2 of therapy she developed dystonic reactions consisting of torticollis and trismus. Her dystonic reaction was reversed by diphenhydramine. However she subsequently complained of left sided weakness and temporary loosening of the teeth.

NMS (1 case)

ISR 38444287 and ISR 38929778 (US)

A 30 year old female received 3 to 5 doses of metoclopramide 10 mg orally over 2 days for nausea after foot surgery. She also received one dose of promethazine⁹ for nausea. On the second day of therapy she experienced dizziness, visual disturbances, hyperthermia, and muscle rigidity. She was treated with diazepam, steroids, and IV fluids in the emergency room. A CT scan was performed which was negative. During the 11 weeks following the drug reaction she made small improvements, but continued to experience severe headaches, fatigue, inability to concentrate, dizziness, disorientation, and nystagmus. MRI and EEG's have all been normal. A neuro-ophthalmologist states that the patient has increased blink rate, and mildly reduced visual acuity which is probably due to the high blink rate and an element of non-organic overlay. Another physician stated that the reaction might have been a dystonic reaction, not NMS and questioned whether the reaction may not have been secondary to a metoclopramide reaction, but to some other medical condition. After a period of symptom improvement starting about 4 months after the reaction and continuing for the next 6 months, the patient now complains of worsening symptoms with frequent visual disturbances and migraine like headaches.

DEATHS, SUICIDES, AND SUICIDAL IDEATIONS

Parkinsons (2 cases)

There were two deaths reported in this case series, one suicide and one death from unknown causes. Neither of these adverse reactions occurred ≤ 3 days after the initiation of therapy.

ISR 978881 (US)

A 48 year old male was prescribed metoclopramide 40 mg QID PO for a hiatal hernia. He also had a past medical history of hypertension; concomitant medications included ranitidine and furosemide. Gradually after the drug was initiated he complained of depression, fatigue, chills, confusion, foot tapping, lip puckering, and mask facies. Approximately 2 months after starting the drug he committed suicide.

ISR 666081 (UK)

A 63 year old woman with a past medical history of diabetes, renal failure, adrenal insufficiency, atrial fibrillation, and hypertension received metoclopramide 40 mg QD for 4 months and subsequently developed tremor, blank face, and cogwheel rigidity. Metoclopramide was discontinued and the tremor improved 2 days later. The patient subsequently died of other causes.

Tardive dyskinesia (2 cases)

⁹ labeled for NMS

No patients died in the case series, but 2 patients complained of suicidal ideation. Neither of these adverse reactions occurred ≤ 3 days after the initiation of therapy.

ISR 3615523 (US)

A 14 year old female was given metoclopramide 10 mg QID for reflux. She had no other medical history; concomitant medication was omeprazole¹⁰. After one month the patient exhibited leg twitching and lip smacking. After 4 months she became depressed and suicidal.

ISR 36691409 (US)

A 45 year old male was given metoclopramide 10 mg QID PO for reflux. Concomitant medications were zolpidem¹¹, omeprazole⁸, fluoxetine¹², and methylphenidate. After 5 months the patient experienced suicidal ideation and was hospitalized.

Akathisia (2 cases)

One patient died in this series and one had suicidal thoughts. Neither of these adverse reactions occurred ≤ 3 days after the initiation of therapy.

ISR 42391264 (Australia)

A 56 year old female with a past medical history of cancer of the bowel was admitted to the hospital for pain control. She was taking metoclopramide (dose and duration unknown), midazolam, morphine, fentanyl, prednisone, ranitidine, amiloride, domperidone, temazepam, docusate, and senna. Approximately 8 months later she developed akathisia, respiratory depression, hepatorenal failure, and vomiting. Midazolam, metoclopramide, and morphine were all discontinued, but the patient subsequently died.

ISR 1411811 (UK)

A patient (age, gender unknown) received metoclopramide (dose, duration unknown) and experienced burning pains, extreme restlessness and became suicidal requiring hospitalization.

Acute dystonia (8 cases)

There were 5 deaths, 1 suicide, and 2 cases involving suicidal ideation in this case series. 4 adverse events occurred within 3 days of starting therapy with metoclopramide; 1 occurred after 4 days and one occurred within 1 week.

¹⁰ labeled for agitation, hallucinations, tremor, anxiety, hemifacial dysesthesia

¹¹ labeled for worsening of depression, including suicidal thoughts in primarily depressed patients

¹² labeled for suicidality in pediatrics and adolescents, although label states that adults should be monitored for the development of suicidal thoughts as well.

ISR 39316954 (US)

Described above under **Summary of Cases** (suicidal ideation).

ISR 31557942 (US)

A 30 month old female received metoclopramide 1.5 mg Q6H IV for nausea and vomiting when she was admitted from the ER for gastroenteritis. Less than 2 days after starting metoclopramide she experienced hyperpyrexia (temperature of 106° F), a shivering episode, crossed eyes, and pinpoint pupils which was diagnosed as oculogyric crisis. She responded to IV diphenhydramine. Antibiotics were started for possible bacteremia. Over the next several hours she remained febrile, was lethargic and tachycardic, and had low oxygen saturation. She subsequently coded and was transferred to the ICU. Upon transfer she had no pulses, BP was 50 systolic and she had purpuric lesions on her lower extremities indicating DIC; she died one day later. Autopsy results indicated no cause or manner of death could be ascertained. The coroner indicated the cause of death was septic shock due to bacterial infection acquired while hospitalized for vomiting and dehydration due to emetine toxicity.

ISR 37840231 (US)

A 39 year old female received 10 mg of metoclopramide PO QID for gastroparesis after being withdrawn from cisapride. After approximately 5 weeks patient experienced severe depression, anxiety, dystonic reactions, and suicide attempt.

ISR 1436524 (Italy)

A 49 year old female with a past medical history of ovarian carcinoma with malignant ascites received metoclopramide IV 60 mg as an antiemetic for chemotherapy (her first time receiving hexamethylmelamine¹³); she had received fourteen previous courses of cisplatin only plus metoclopramide with no adverse reaction. One hour after metoclopramide administration she experienced vertigo, tremors and speech impairment. She was treated with orphenadrine. The patient then received the intraperitoneal cisplatin¹⁴. Two hours later the patient experienced a dystonic reaction with facial spasms, trismus, torticollis, and oculogyric crisis. The patient was given orphenadrine and diazepam. Thirty minutes later she experienced another dystonic reaction followed by two more episodes. Five hours later she experienced cardiorespiratory arrest and died.

ISR 766537 (US)

A 58 year old female with past medical history of cerebral palsy that resulted in moderately severe mental retardation and tremor was treated with prochlorperazine and

¹³ This antineoplastic drug is not approved in the US, but has been reported to cause adverse events such as ataxia, vertigo, and Parkinson like tremors.

¹⁴ Labeled for severe involuntary muscle spasms with high dose cumulative therapy

metoclopramide 10 mg QID PO for gastroenteritis and emesis. Over the following week she developed lethargy and rigidity and was hospitalized. On admission she was diagnosed with a UTI and pneumonia; metoclopramide was continued. Twenty days later she was noted to be totally bedridden with blepharospasm and increased muscle tone in all extremities. She was unsuccessfully treated with carbidopa/levodopa. Metoclopramide was discontinued approximately 45 days later and she was treated with trihexyphenidyl; her dystonia did not improve. Approximately 1 month later she had recurrent pneumonia, UTI, and line infections; she remained bedridden. Approximately 2 months later she experienced a sudden rise in temperature and died. Autopsy revealed chronic bronchiolitis, fatty degeneration and passive congestion of the liver, chronic pyelonephritis, old myocardial infarction, and shrunken neurons in the midbrain with expansion of the perineuronal spaces.

ISR 639906 (US)

A 63 year old male was treated with metoclopramide 20 mg QD PO for reflux for 1 month and developed depression anxiety, anorexia, nervousness, and involuntary arm movement. Concomitant therapy included cimetidine. Patient committed suicide 4 months after initiating metoclopramide therapy.

ISR 1448292 (UK)

A 71 year old male undergoing cholecystectomy received metoclopramide 40 mg daily PO for post operative (16 days post procedure) nausea. He had a past medical history of sigmoid colectomy for carcinoma and intermittent jaundice. Four days after initiating metoclopramide he became agitated; he was also jaundiced. Several hours later he experienced a dystonic reaction, tremors, and hypotension. Prochlorperazine was administered. Several hours later the patient went into asystole and was unable to be resuscitated. Autopsy revealed cerebral edema and arterial atherosclerosis.

ISR 479900 (Denmark)

An 84 year old woman received metoclopramide 10mg IV and chlorpromazine¹⁵ 25 mg IV for abdominal pain. Thirty minutes later she developed arm spasms, abnormal respirations, and lock jaw. Biperiden was administered, but had no effect; the patient lost consciousness. The symptoms were relieved by diazepam 20 mg, but she died 36 hours later. Autopsy showed a subdural hematoma and tentorial incarceration.

NMS

There were 8 deaths in this case series. Two of the adverse events occurred ≤ 3 days after initiation of metoclopramide; in two cases the timeline was unknown. The remaining events occurred 5, 7, 8 and 15 days after metoclopramide initiation.

ISR 1926263 (US)

¹⁵ labeled for extrapyramidal symptoms

A female patient (age unknown) received metoclopramide (route, dose, duration, indication unknown) experienced febrile seizures and was prescribed diphenhydramine. Patient was receiving prolonged antibiotic treatment for an immunocompromised condition. Approximately 8 days after exposure to metoclopramide (unknown if chronic or one time therapy), the patient experienced respiratory failure, pyrexia, liver and kidney deterioration. Cardiac arrest occurred and the patient died.

ISR 34600169 (US)

A patient (age, gender unknown) “may have” received oral metoclopramide (dose, duration, indication unknown) and experienced neuroleptic malignant syndrome and died.

ISR 758290 (UK)

A 32 year old female with past medical history of advanced carcinoma of the cervix received prochlorperazine¹⁶ then haloperidol¹⁶ for persistent nausea. Metoclopramide 10 mg TID was added to her regimen. Over 48 hours the patient developed spiking fevers, became hypertonic, withdrawn, diaphoretic, tachycardic, and tachypnic. Metoclopramide and haloperidol were discontinued 5 days later. The hypertonicity resolved over 2 to 3 days, but she remained withdrawn. Eight days later she was started on amitriptyline, domperidone, and cyclizine. Four days later she experienced cardiopulmonary arrest and died.

ISR 736401 (US)

A 60 year old male with a medical history of sepsis, ARDS, and pancreatic cancer received metoclopramide 10 mg IV Q6H for increased gastric motility. Concomitant medication included droperidol¹⁴. After 5 days he developed cogwheel rigidity, high temperature (104° F), and was obtunded. He was treated with diphenhydramine and dantrolene. He remained rigid for 3 days and subsequently died 4 days later.

ISR 833420 (France)

A 65 year old patient (gender unknown) was treated with metoclopramide 10 mg IV experienced neuroleptic malignant syndrome and died. No other information is available.

ISR 34476933 (US)

A 67 year old male received metoclopramide 10 mg IV Q6H for treatment of GI bleed. Two days later he experienced increased agitation, restlessness, and high temperature - 106.4°. Dantrolene, acetaminophen, and lorazepam, and cooling blanket initiated and patient’s temperature improved. Patient died 2 days later from GI bleed and sepsis.

¹⁶ labeled for NMS

ISR 1997175 (US)

A 74 year old male received metoclopramide 10 mg Q6H PO for an unknown indication. He had a complicated medical history including diabetes, sepsis, ARDS, acute renal failure, and ventilator dependence. Concomitant therapy included cyclobenzaprine¹⁷. Approximately 15 days after starting metoclopramide, in the process of weaning from the vent, he experienced shortness of breath, emesis, tremors and chills. The patient's temperature was 104° but rapidly increased to 107°. He was treated with lorazepam, external cooling, diphenhydramine, and dantrolene. His temperature rapidly decreased. Over the next several hours his blood pressure dropped, he developed shock, and then died.

ISR 1365695 US

A 77 year old male was treated with metoclopramide 10 mg (frequency unknown) along with cisapride¹⁸ for treatment of loss of appetite. After 1 week he noticed stiffness in his legs and became increasingly immobile and depressed. After 5 weeks he was admitted to the hospital for treatment of fever, leukocytosis, muscle rigidity, tachycardia, and tachypnea. He subsequently died. Autopsy showed aspiration of vomit was cause of death.

DISCUSSION

The characteristics of the cases retrieved from the AERS database involving movement disorders and NMS related to metoclopramide use reinforce what has been shown in the literature and product labeling regarding these adverse events. For the most part, the movement disorders are reversible over time. Unfortunately, some patients continue to have symptoms or recover with sequelae after the drug has been discontinued; most of these cases are associated with chronic (>30 days) therapy with metoclopramide.

When considering this new indication of metoclopramide (treatment of acute migraine), in which the nature of the drug regimen is intermittent and not chronic, it is important to ensure that this type of therapy possesses a favorable risk/benefit ratio; an excess risk of irreversible movement disorder and NMS would be unacceptable. There is a dearth of data in AERS specifically involving adverse events related to intermittent use of metoclopramide, however the following information is relevant:

- Most of the adverse events where the symptoms were continuing at the time of reporting involved chronic therapy (>30 days of continuous use-with the exception of acute dystonia)
- There were few (8) cases involving adult patients in which short term therapy (≤ 3 days) led to continuing symptoms. Most of these cases involved 3 or more doses before the adverse event occurred. In only one of these cases did the reaction occur after one dose and no information was provided regarding dose or route of

¹⁷ labeled for hypertonia

¹⁸ not approved for general use in the US. Cisapride has been associated with NMS.

administration (ISR 1584424). In another case where the reaction occurred after 2 doses of 20 mg oral metoclopramide, the dystonia resolved with diphenhydramine. The continuing symptoms were left sided weakness and temporary loosening of the teeth, not symptoms consistent with dystonia.

- There were 15 deaths in the case series.
 - The duration of metoclopramide therapy before death occurred ranged from 1 dose to 8 months
 - In the majority of these cases the patient had a concomitant disease (cancer, sepsis) that could have contributed to the death.
 - In many of the cases the patient was on concomitant medications (haloperidol, cyclobenzaprine) which could have contributed to the adverse event
- There were 5 patients who experienced suicidal ideation
 - The duration of metoclopramide therapy before suicidal ideation occurred ranged from 3 doses to 5 months
 - One patient was on a concomitant antidepressant
- There were 2 suicides
 - The duration of metoclopramide therapy before suicide ranged from 2 to 4 months

Some points to consider when evaluating the safety profile of Myzan include characteristics of usage with the currently available metoclopramide product and patterns of treatment with other migraine therapies. Metoclopramide is used for a number of off-label indications (including analgesia and migraine headache). Current usage patterns, particularly focusing on these therapeutic uses, may elucidate how metoclopramide may be presently being utilized for treatment of migraines¹⁹. Moreover, use patterns for other modalities used to treat and prevent migraine headaches (triptans, ergots, caffeine, SSRI's, etc.) may also indicate how Myzan may be used clinically, if it were to become commercially available. Although the proposed labeling for Myzan allows for only intermittent dosing of the drug (one tablet per migraine, no second dosing, up to 6 doses per month), it is possible that patients may use the drug in a (off-label) manner similar to some other migraine treatments (chronically, for prophylaxis) The data from AERS suggests that movement disorders would be a valid risk associated with this type of treatment.

CONCLUSION/RECOMMENDATION

The characteristics of the movement disorders and NMS related to metoclopramide use observed in the cases from the AERS database correlate well with what has been reported in the literature. There were no cases in AERS which presented movement disorders (reversible or otherwise) or NMS with intermittent use of metoclopramide. It is unknown whether this is because this dosing regimen typically does not occur, or, if it does, very few adverse events have occurred (or been reported) because of it.

¹⁹ Separate consult by Division of Surveillance, Research, and Communication Support.

Data on irreversible movement disorders and NMS relating to short term use (≤ 3 days) of metoclopramide reveals only a small number of reported cases. In addition, there are relatively few deaths/suicides attributed to metoclopramide alone and in most of these cases, the patient had concomitant diseases or medications which could have contributed to the outcome.

In conclusion, we do not believe the safety data from the AERS database preclude the proposed use of occasional metoclopramide for the treatment of acute migraine. According to data in the AERS cases, the occurrence of irreversible movement disorders and NMS is largely a risk associated with chronic use of metoclopramide. From information that has been provided in the AERS reports it is not possible to differentiate risk associated with chronic (frequent) intermittent treatment compared to chronic continuous treatment. A separate concern that has been raised by this analysis is the potential for drug – drug interactions that enhance the likelihood of acute dystonic reactions, even after short-term use.

Signed,

Mary Ross Southworth, PharmD, Safety Evaluator

Concur,

Cindy Kortepeter, PharmD, Team Leader

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/s/

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