MEMORANDUM

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Metoclopramide: Drug Use Data Review
(Myzan®, NDA 21-645)

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EXECUTIVE SUMMARY

This consult examines outpatient prescribing and drug use patterns for metoclopramide in the U.S. as well as the duration of therapy for this drug using longitudinal patient level data.

Metoclopramide is a neuroleptic dopamine receptor antagonist, currently marketed in the U.S. (Reglan®) for short-term therapy of gastroesophageal reflux and for treatment of diabetic gastroparesis. In general, therapy with metoclopramide tablets should not exceed 12 weeks in duration, as prolonged therapy and cumulative dose may increase the risk of developing tardive dyskinesia. The aim of this review is to assist in preparation for a forthcoming advisory committee meeting on the approvability of Myzan®, a combination of naproxen and metoclopramide, for the acute treatment of migraine, by estimating both the use of metoclopramide in the U.S. as well as the proportion of patients taking metoclopramide for more than 90 days.

The consult includes the following two sections:

I. National Utilization Patterns of Metoclopramide

Description

The first section describes the utilization patterns of metoclopramide in the U.S. in a ten-year period from 1995-2004. This includes national estimates of physician office visit characteristics associated with the prescription of metoclopramide, such as patient's age, gender, indication for use and prescriber specialty information. Data for this section were derived from cross-sectional outpatient data from IMS Health audits (IMS Health, National Prescription Audit *Plus*™ [NPA *Plus*™] and IMS Health, National Disease and Therapeutic Index™ [NDTI™]), proprietary drug use databases licensed by the Agency.

Results

Over the ten-year period from 1995 to 2004, there was a two-fold increase in the number of outpatient prescriptions dispensed for metoclopramide in the U.S. In 1995, the number of prescriptions dispensed for metoclopramide was almost 3.5 million. This number declined to less than 2 million prescriptions dispensed annually from 1997 to 1999, and then increased abruptly in 2000 and reached over 7 million prescriptions dispensed during 2004. The increase in dispensed prescriptions beginning in 2000 is likely due to the withdrawal of cisapride, a treatment for severe nighttime heartburn, from the U.S. market in March 2000. Almost 90% of the metoclopramide products dispensed were in an oral tablet dosage form.

Over one-third of the annual visits in the U.S., in which metoclopramide was mentioned, were made by patients ages 35-64 years old. Elderly patients (aged 65 years and older) accounted for about a third of the visits in which metoclopramide was mentioned from 1995-1998, yet their proportions declined steadily in the subsequent years. As opposed to the elderly population, visits in which metoclopramide was mentioned in the pediatric population (aged 0-16 years) increased steadily throughout the ten-year study period and constitute more than 30% of these visits in 2004. Visits in which metoclopramide was mentioned in patients aged 17- 34 years remained steady. On average, over 55% of the annual visits in which metoclopramide was mentioned were made by females.

During the last five years, from 2000 through 2004, more than 50% of metoclopramide uses were for gastroenterology-related diagnoses. "Esophagitis" (ICD-9 code 530.1) was ranked the most common diagnosis for metoclopramide mentions, accounting for over 40% of metoclopramide mentions.

During 2004, internal medicine was the most frequent prescribing specialty, accounting for over 1.2 million (22%) dispensed prescriptions for metoclopramide, followed by family practice (18%) gastroenterology (13%), osteopathic medicine (8%) and pediatric practice (5%).

II. Duration of Therapy for Metoclopramide

Description

The second section depicts patient characteristics and duration of therapy for metoclopramide in a large insured population whose prescription drug benefits were managed by Caremark in a three-year period from 2002-2004. Longitudinal data for this section were derived from outpatient claims data from Caremark's Dimension Rx™, a proprietary drug use database licensed by the Agency at the time of this study.

Methods

The study population consisted of individuals aged 1-99 years who were continuously eligible in the Caremark pharmacy benefit manager (PBM) database and had prescription claims for any metoclopramide products between January 1, 2002 to December 31, 2004. Claims were excluded from this analysis based on pre-determined exclusion criteria. The final data analysis was performed on a subset of 200,907 patients with 572,205 prescription claims for metoclopramide tablets.

Claims data for this subset of the study population were used to determine an episode of metoclopramide therapy for an individual. An episode of therapy was defined as one or a series of consecutive prescription claims for metoclopramide for an individual with no more than a 30-day lag between a new prescription and the ending date of the preceding prescription. The duration of each episode of therapy was calculated for each episode by summing up the total days' supply from claims that constituted that episode. The duration time lag between the claims was not included in the calculation of the duration of therapy. The duration of the longest episode for metoclopramide was determined for each patient. Cumulative exposure to metoclopramide during the study period was estimated for each patient by summing the duration of each episode.

Three sensitivity analyses were performed to examine the robustness of the assessment of duration of therapy, duration of the longest episode of therapy as well as the cumulative exposure.

Results

Prescriptions claims for metoclopramide were almost exclusively filled by adults, 50% of which were persons aged 35-64 years. The mean age of the study population was 58 years old (standard deviation (SD) =17.9). About two-third of the claims were filled by females and only one-third by males. Approximately one-half of the claims were filled in pharmacies located in the southern region in the U.S.

The average number of prescriptions for metoclopramide per patient was 2.8 (SD=4.7). The majority of the patients (66%) had only one paid prescription claim for metoclopramide. The length of the longest episode of therapy for most patients (87%) varied from 1 to 90 days, yet about 13% of the patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days.

For the majority of the patients in the study (68%), the length of cumulative therapy for metoclopramide was 1 to 30 days. The frequency of patients decreased as the total cumulative therapy for metoclopramide increased. Nonetheless, the frequency of patients who had cumulative therapy for metoclopramide for more than 6 months exceeded 10%.

A sensitivity analysis of the duration of the longest episode and cumulative therapy for individuals whose claims were for 100 days of supply or less reveals that there was no significant change from the result presented above.

Conclusions

Results from this study indicate that the number of prescriptions dispensed for metoclopramide, which were declining from 1995 to 1999, have more than tripled in the five-year period following the withdrawal of cisapride from the U.S. market in March 2000. In addition to this increase in the U.S. in recent years, data from an insured population source showed that over 10% (10-15%) of metoclopramide users, had paid claims suggesting use for a period longer than the three months recommended in the label. Moreover, data suggestive of total cumulative therapy with metoclopramide longer than 6 months was found in about 10% of the study population.

The increase in the number of prescriptions dispensed for metoclopramide along with the longer than recommended duration of use found in this study was substantial. These findings suggest that even in light of metoclopramide label restrictions on the duration of use and its well-recognized adverse events, particularly extrapyramidal movement disorders, physicians as well as patients did not follow the labeled recommendation for limited duration of therapy. These results suggest that a similar label recommendation for a new combination product that contains metoclopramide is not likely to be followed, especially if the product contains naproxen, which is frequently used without restrictions on duration.

INTRODUCTION

In May 2003, the Division of Neuropharmacological Drug Products within the Office of New Drugs issued a Not Approvable letter for a New Drug Application (NDA) for Myzan® (formerly MT100, NDA 21-645), a combination of naproxen and metoclopramide for the acute treatment of migraine. The letter was issued because the agency found that the sponsor did not establish the contribution of metoclopramide to the efficacy of the product combination. Furthermore, a major safety concern was raised due to the risk of movement disorders (parkinsonism, akathisia and acute dystonia), well-known to be associated with metoclopramide hydrochloride.

In late 2004, the sponsor submitted additional data in order to demonstrate that metoclopramide seemed to provide a significant improvement in a subgroup of migraine patients with no nausea at baseline. This effect seems counter-intuitive since one would expect that the pharmacological effect of such an antiemetic drug would be expressed and the drug would show effectiveness in patients with nausea. Regardless of the unexpected effect of this antiemetic drug, the division may agree to grant an indication for treatment of migraine in that subpopulation, if the sponsor prospectively replicates that finding and demonstrates that the clinical benefit outweighs the risk of tardive dyskinesia (TD) and other movement disorders associated with metoclopramide.

However, before the sponsor conducts an additional efficacy study, an advisory committee (AC) meeting is scheduled to determine if the risk of TD with chronic intermittent use of metoclopramide is sufficiently high to preclude approval of the drug for a migraine indication, even if the efficacy study to be conducted shows an effect in the subpopulation of non-nauseated patients.

The Division of Surveillance, Research and Communication Support (DSRCS) within the Office of Drug Safety (ODS) was consulted by the Division of Neuropharmacological Drug Products within the Office of New Drugs to assist in the preparation for this advisory committee meeting on the approvability of Myzan® for the acute treatment of migraine. DSRCS was requested to examine the use of metoclopramide products in the U.S. and provide information on the following:

- Estimate and characterize the use of metoclopramide in the U.S. over the past 10 years
- Examine use patterns to determine whether physicians and patients follow the labeled recommendations with regard to the restriction on duration of therapy, and to specifically determine the proportion of patients whose pattern of paid prescription claims suggests that they received treatment for a longer period than the three months specified in the label.

This review describes outpatient prescribing and drug use patterns for metoclopramide in the U.S. and examines the duration of therapy for this drug in longitudinal patient level data. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

BACKGROUND

Metoclopramide is a neuroleptic dopamine receptor antagonist, currently marketed in the U.S. (Reglan®) for short-term therapy (4 to 12 weeks) of gastroesophageal reflux, only when conservative treatment fails, and for treatment of diabetic gastroparesis (2-8 weeks). It is available in three dosage forms: oral tablets, oral solution and injection. The recommended administration regimen of the oral tablets for the relief of symptomatic gastroesophageal reflux is 10 mg to 15 mg metoclopramide up to four times a day, and for the relief of symptoms associated with diabetic gastroparesis (diabetic gastric stasis) – 10 mg of metoclopramide before each meal and at bedtime for two to eight weeks. In general, therapy with metoclopramide tablets should not exceed 12 weeks in duration. Reglan® (metoclopramide) labeling states that patients treated with metoclopramide may develop tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements. The label states that the risk increases with the duration of treatment and the cumulative dose.

A review of the medical literature supports that metoclopramide is associated with TD as well as with other movement disorders.[1-5] Moreover, it was suggested that metoclopramide-induced TD can be permanent.[6] However, this type of side effect can only be expected to be observed when large populations are exposed to the drug for a long time period, and not during the relatively short drug development process, such as the one for Myzan® (where no case was reported in the NDA). Therefore, the absence of cases of tardive dyskinesia in the Myzan® trial is not indicative that this adverse reaction will not occur, but rather that the trial duration was likely too short to detect such a safety problem. 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 months.[4] 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.

In addition to the increased risk of tardive dyskinesia, metoclopramide is associated with other neurological and psychiatric symptoms. Tardive tremor due to metoclopramide was recently described.[5] There is also a warning in Reglan® labeling about a risk for depression,[7-9] suicidal ideation and suicide. Finally, the label reports rare cases of neuroleptic malignant syndrome, which is potentially fatal.

The exact incidence of metoclopramide-induced tardive dyskinesia remains unclear, but based on the medical literature long-term use of metoclopramide should be avoided to prevent persistent and disabling movement disorders. Two factors potentially mitigating the risk of tardive dyskinesia in the case of Myzan® are the recommended intermittent use and the relatively low dose of metoclopramide.

Since metoclopramide-induced tardive dyskinesia is associated with prolonged use of the drug, it was hoped that an examination of utilization patterns and duration of use of metoclopramide products currently on the market would shed light on the extent of off-label prescribing and use of metoclopramide, which could have implications for a new metoclopramide-contained product. Specifically, the duration of use of metoclopramide is important in determining cumulative drug exposure, extent of adherence to the label recommendations and the risk of such adverse drug events in metoclopramide users. Duration of use longer than recommended in the label may suggest that the risk of Myzan® if approved, may outweigh the benefit of the drug. Any excess

risk from prolonged exposure to metoclopramide should be avoided, especially when alternative migraine products are available in the market.

METHODS

I. National Utilization Patterns of Metoclopramide

Outpatient use of metoclopramide was derived from several data sources. IMS Health, National Prescription Audit *Plus*™ (NPA *Plus*™) was used to examine dispensed prescriptions of metoclopramide in the U.S. focusing on the outpatient setting. IMS Health, National Disease and Therapeutic Index™ (NDTI™) was further used to describe the prescribing patterns of metoclopramide among physicians, patient characteristics, and the indications for which the drug was prescribed.

The data sources for this analysis are described in detail below.

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis include prescriptions dispensed for metoclopramide products for the last ten-year period from January 1, 1995 – December 31, 2004, inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental U.S. The data are collected from a panel of roughly 2,000 – 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned and treatment patterns. The data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of metoclopramide during office-based physician visits during the last ten-year period from January 1, 1995 – December 31, 2004, inclusive.

II. Duration of Treatment for Metoclopramide

Paid prescription claims for a 36-month period of time from Caremark (Dimension Rx™) provided a longitudinal data source for estimating the duration of therapy with metoclopramide. The data source for this analysis is described in detail below.

CAREMARK, DIMENSION RX™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million lives, and processing over 545 million prescription claims annually. FDA had access to Caremark's Dimension Rx™ database consisting of a subset of total Caremark paid claims, representing 350 million claims per year for prescriptions filled in 57,000 pharmacies across the country. These participant-level claims are available for 36 rolling months at the time they are accessed on-line. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's Dimension Rx™ system includes participants from all 50 states including special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark's Dimension Rx™ system to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims for metoclopramide generic products in the Caremark Dimension Rx™ system were examined for all persons aged 1-99 years from January 1, 2002 to December 31, 2004, inclusive.

Study Population

The study population consisted of individuals aged 1-99 years who were continuously enrolled in the Caremark PBM and had prescription claims for any metoclopramide products between January 1, 2002 to December 31, 2004. The original dataset contained 611,951 prescription claims for metoclopramide for 209,641 individuals during the study period. This dataset was examined for data inconsistency and accuracy. Claims were excluded from this analysis if they had either quantity or days' supply that was either "unknown" or was assigned a value of zero. Of the remaining claims, individuals were excluded if they had multiple claims with a greater than two-year lag time in patient age between two consecutive prescriptions. Also, individuals were excluded if the value of gender assigned was not consistent across their associated claims or if it was assigned as "unknown". Individuals for whom the drug quantity in the metoclopramide claims was not a whole number were removed. As a result of these exclusions, less than 2% of the original claims and the original individuals were removed. The final dataset consisted of 601,226 prescription claims for metoclopramide for 207,688 patients. From this data set we extracted a subset of individuals that had claims for metoclopramide tablets only. Our analysis pertains to this subset of 200,907 individuals only. The design and the exclusion criteria for the study sample are illustrated in the diagram scheme in Figure 1.

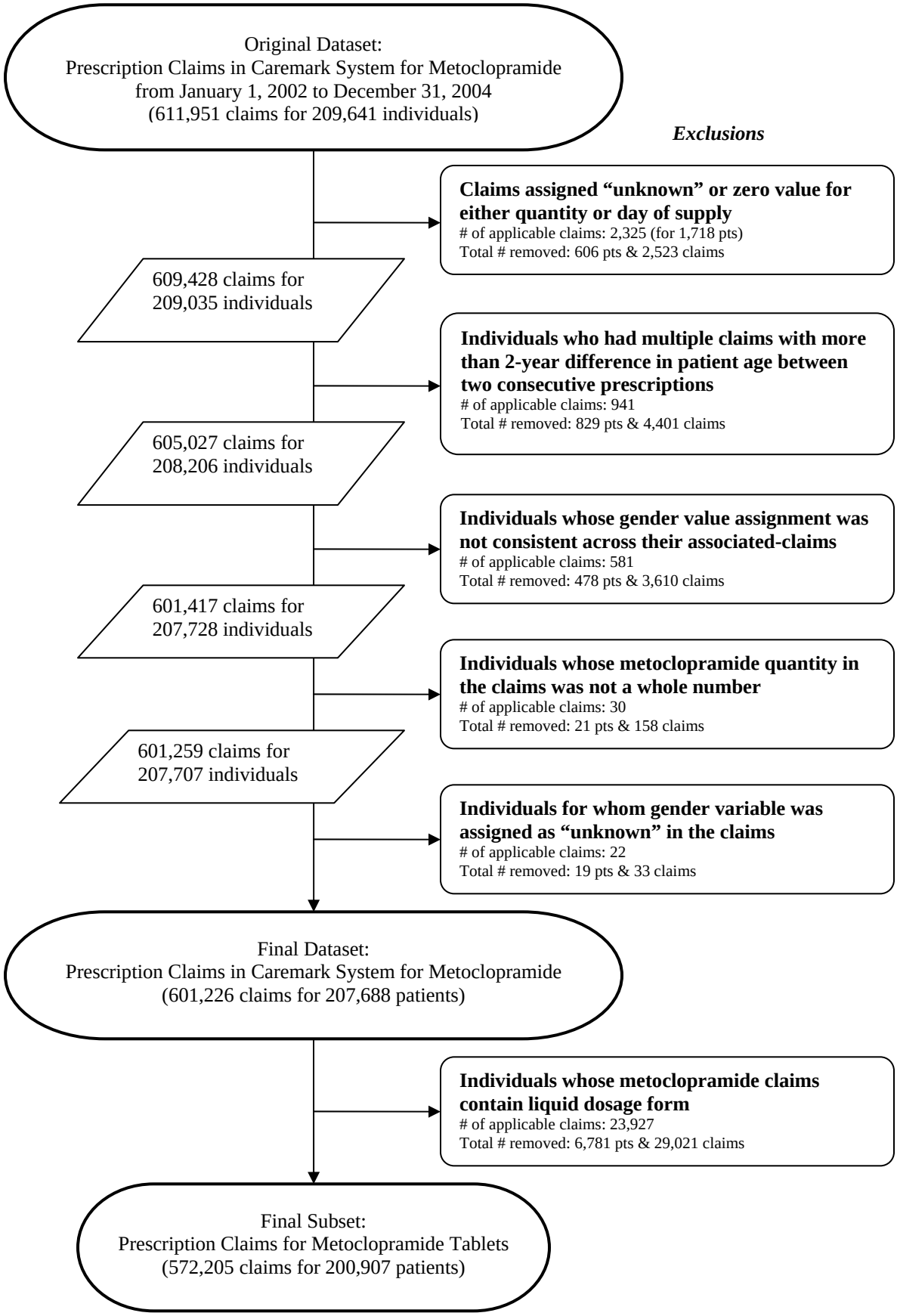

Figure 1. Design and Exclusion Criteria for the Study Sample of Prescription Claims Filled for Metoclopramide, Caremark Dimension Rx™, 2002 - 2004

Measurements

Claims data for this subset of the study population were used to determine an episode of metoclopramide therapy for an individual. The episode of therapy was constructed based on an algorithm that was previously developed in DSRCS. We defined an episode of therapy as one or a series of consecutive prescription claims for metoclopramide for an individual with no more than a 30-day lag between the dispensing date of a new prescription and the ending date of the preceding prescription. The ending date of a prescription was calculated for each prescription by adding the number of days' supply to the claim date. A successive prescription for the same patient, that was dated more than 30 days after the ending date of the preceding prescription, was not considered part of the previous episode and was considered as the onset of a new episode of therapy.

The duration of each episode of therapy was calculated for each episode by summing up the total days' supply from claims that constituted that episode. The time lag between the claims was not taken into account in calculating duration of episode of therapy. The duration of the longest episode for metoclopramide was determined for each patient. Cumulative exposure to metoclopramide during the study period was estimated for each patient by summing the duration of each episode.

The age of the patient was calculated from the date of birth and was defined as the age at first prescription as we allowed individuals to age during the study period or to have age difference of ±2 years from claim to claim.

We determined the region in which the prescription claims for metoclopramide were filled by categorizing the pharmacy state information into four regions as designated by the U.S. Census Bureau: Northeast, Midwest, South, and West.[10] We created another category "other" which included Puerto Rico, Virgin Islands, Northern Mariana Islands, and Guam.

Analytic Methods

All analyses were performed using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC). The following sensitivity analyses were performed to examine the robustness of the assessment of duration of the longest episode of therapy as well as the cumulative exposure:

- *Excluding individuals with extreme values of days' supply.* In this analysis we only included individuals that had 100 days' supply or less. The 100-day cut-off was used as many health insurance companies do not cover the cost of prescriptions that exceed 100 days' supply. We recalculated the duration of the longest episode of therapy and the mean cumulative exposure for these individuals.
- *Redefining episode of therapy.* We used the original study population and redefined the episode of therapy based on no more than a 10-day lag between the dispensing date of a new prescription and the ending date of the preceding prescription. We recalculated the proportion of individuals with an episode of metoclopramide therapy longer than 90 days.
- *Redefining the total duration of episode of therapy.* In the third analysis, we used the original study population and redefined the total duration of therapy for an episode to include the time lag between prescription claims.

RESULTS

I. National Utilization Patterns for Metoclopramide

A. Prescriptions dispensed for Metoclopramide, 1995-2004

Over the ten-year period from 1995 to 2004, there was a two-fold increase in the number of outpatient prescriptions dispensed for metoclopramide in the U.S. (Figure 2). At the beginning of that period in 1995, the number of prescriptions dispensed for metoclopramide was almost 3.5 million. It declined to less than 2 million prescriptions dispensed annually from 1997 to 1999, and then increased abruptly in 2000 and reached over 7 million prescriptions dispensed during 2004. The increase in dispensed prescriptions beginning in 2000 is likely due to the withdrawal of cisapride, a treatment for severe nighttime heartburn, from the U.S. market in March 2000.

Almost 90% of the metoclopramide products dispensed were in an oral tablet dosage form; over 10% were in the syrup dosage form and less than 1% were injectables in each of the one-year periods from 2000 to 2004.

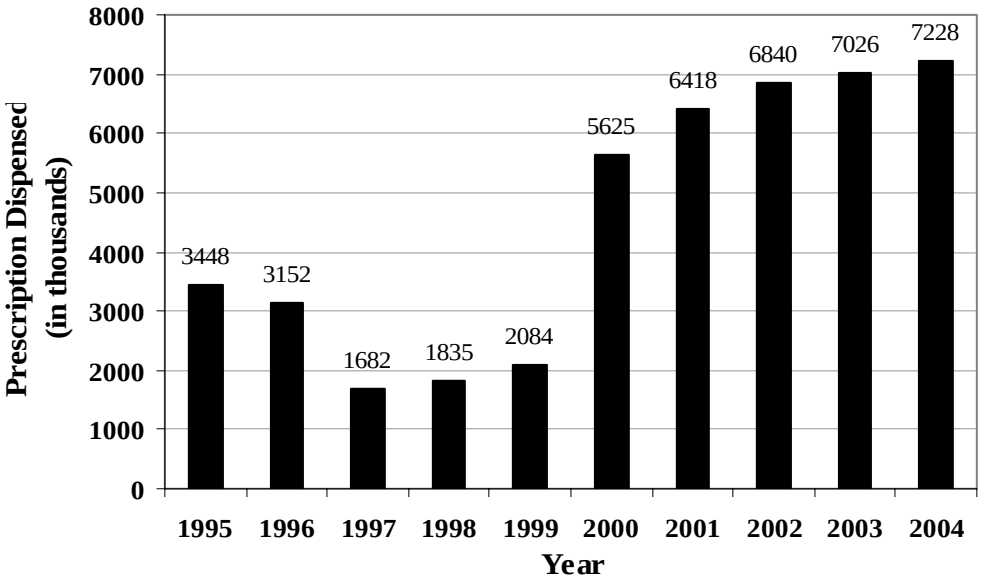

Figure 2. Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Metoclopramide Products, IMS Health, NPA *Plus*™, 1994 – 2004

Source:
1995-1996 IMS Health, National Prescription Audit *Plus*™ book data- Dec 1996, USC 01200-33390
1997-1999 IMS NPA CD-ROM Dataview Analyzer Total Market CD-ROM
Years 2000 - 2004, extracted February 2005.

B. Visit Characteristics of Metoclopramide, 1995-2004

During the ten-year period from 1995 through 2004, NDTI™ recorded an average of 1.4 million mentions of metoclopramide annually during physician-office visits made in the U.S. (data not shown). Similar to the prescription data, visits with mentions of metoclopramide decreased from 1.5 million visits during 1995 to 1.0 million visits during 1999, and increased back again to 1.5 million visits during 2004.

Oral Metoclopramide and Age

Over one third of the annual visits in the U.S., in which metoclopramide was mentioned, were made by patients ages 35-64 years old during the ten year period from 1995 to 2004 (Figure 3). While elderly patients (aged 65 years and older) accounted for about a third of the visits in which metoclopramide was mentioned from 1995-1998, their proportions declined steadily in the subsequent years. In 2004 they accounted for only 20% of the visits in which metoclopramide was mentioned. The proportions of the visits in which metoclopramide was mentioned in patients aged 17- 34 years remained steady from 1995 to 2004. As opposed to the elderly population, in which we detected a decline in the visits in which metoclopramide was mentioned, the proportion of these visits in the pediatric population (aged 0-16 years) increased steadily throughout the ten-year period of the study from 10% of all visits in which metoclopramide was mentioned in 1995 to more than 30% in 2004.

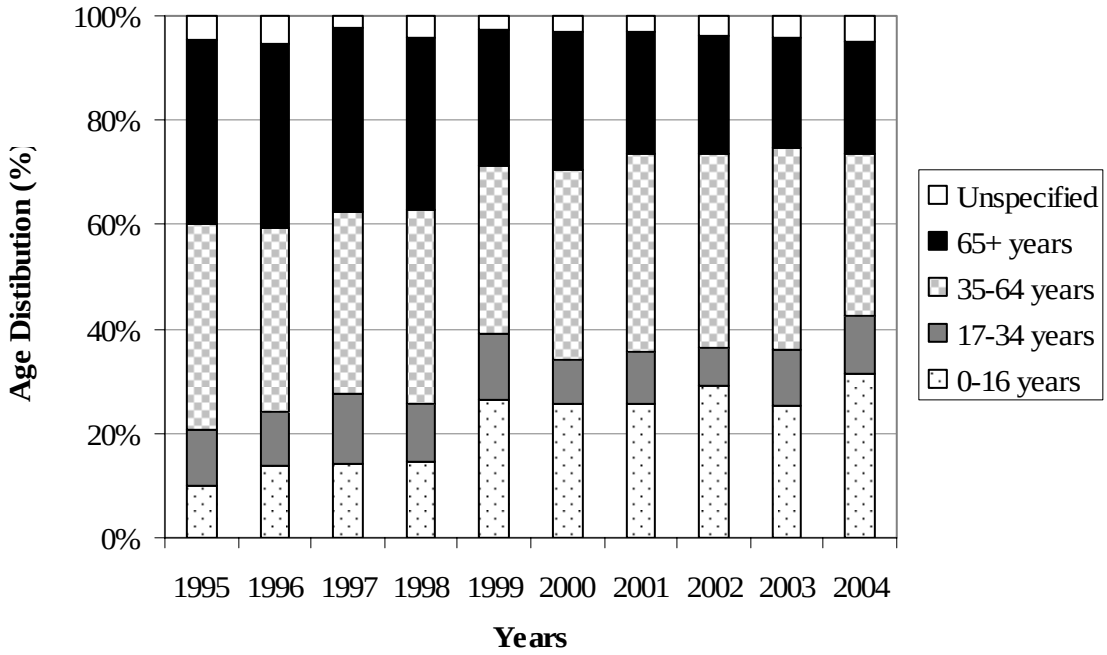

Figure 3. Age Distribution of Visits in which Metoclopramide was mentioned in the U.S., IMS Health, National Disease and Therapeutic Index™, 1995 - 2004

Oral Metoclopramide and Gender

From 1995 to 2004, on average over 55% of the annual visits in which metoclopramide was mentioned were made by females (Figure 4).

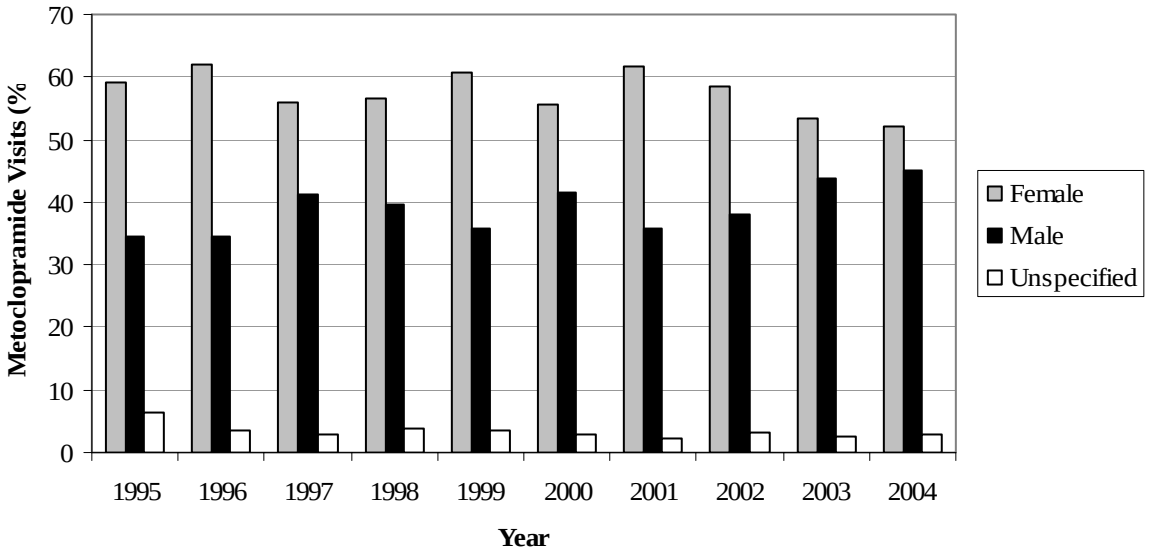

Figure 4. Distribution of visits in which Metoclopramide was mentioned by gender in the U.S., IMS Health, National Disease and Therapeutic Index™, 2000 - 2004

Oral Metoclopramide and Indication for Use

During the last five-year period from 2000 through 2004, more than 50% of metoclopramide uses were for gastroenterology-related diagnoses (data not shown). "Esophagitis" (ICD-9 code 530.1) was ranked the first most common diagnosis for metoclopramide mentions, accounting for over 40% of metoclopramide mentions (Table 1). The two top indications for metoclopramide drug uses after "esophagitis" were "post-surgical examination" (v670), with more than 6% of metoclopramide mentions and "nausea and vomiting" (ICD-9 code 787.0), with about 5% of mentions. Other diagnoses each accounted for less than 5% of the total metoclopramide mentions, including "gastroparesis" (536.3 or 250.6 - diabetes with neurological manifestations), which accounted for less than 1% of all indications mentioned in 2004. In general, diagnoses associated with mentions of metoclopramide showed relatively little change across the years. Notably, "migraine unspecified" was a diagnosis consistently associated with mention of metoclopramide since 2000, although in less than 2% of visits. Given the small number of visits this projection is based upon, it should be viewed with caution.

Table 1. Diagnoses Associated with Mentions of Metoclopramide During Office-Based Physician Visits, IMS Health, National Disease and Therapeutic Index™, 2000 – 2004

2004 Drug Uses Rank	Diagnoses	Drug Uses (%)				
		2000	2001	2002	2003	2004
		(n=1,549,000)	(n=1,715,000)	(n=1,559,000)	(n=1,527,000)	(n=1,480,000)
1	530.1 ESOPHAGITIS	43.6	43.3	48.0	48.5	42.3
2	V67.0 POST SURGERY EXAM	6.9	6.6	8.1	6.0	5.7
3	787.0 NAUSEA AND VOMITING	8.0	6.4	6.7	2.3	4.5
4	009.1 COLITIS, ENTERITIS, GASTROENTERITIS OF PRESUMED INFECTIOUS ORIGIN	1.2	0.8	1.9	4.7	3.7
5	352.2 OTH DISORDERS OF GLOSSOPHARYNGEAL NERVE	4.1	2.1	2.8	2.4	3.6
6	008.8 OTH ORGANISM, NOT CLASSIFIED	---	---	0.2	0.4	3.0
7	789.0 ABDOMINAL PAIN	2.6	6.2	4.4	2.7	2.8
8	536.8 DYSPEPSIA+DISORDERS OF FUNCTION OF STOMACH	2.8	1.8	0.9	1.4	2.8
9	535.5 UNSPECIFIED GASTRITIS+GASTRODUODENITIS	2.2	1.7	2.6	1.5	2.5
10	250.5 DIABETES WITH NEURO MANIFEST	3.2	3.4	2.6	1.7	2.3
11	346.9 MIGRAINE UNSPECIFIED	0.8	1.6	1.8	1.0	1.8
12	799.9 OTH UNKNOWN+UNSPEC CAUSE	1.0	1.0	1.3	0.5	1.6
13	564.1 IRRITABLE COLON	0.4	1.2	0.4	1.0	1.5
14	779.3 FEEDING PROBLEMS NEWBORN	1.1	1.1	0.7	---	1.5
15	560.1 PARALYTIC ILEUS	0.7	0.9	0.3	---	1.3
16	643.0 MILD HYPEREMESIS GRAVID	0.6	0.2	0.3	0.7	1.2
	Other Diagnoses *	20.6	21.6	17.0	25.2	17.9

IMS Health, National Disease and Therapeutic Index™, Years 2002 – 2004, Extracted March 2005.
Original File:
* Includes diagnoses which are less that 1% of total metoclopramide mentions

During the ten-year period from 1995-2004, the proportion of office-based visits for the pediatric population increased (from 10% in 1995 to 30% in 2004) along with the increase in the "esophagitis" diagnosis (from 35% in 1995 to 65% in 2004) (data not shown). As of 2000, "esophagitis" (ICD-9 code 530.1) accounted for more than two-thirds of all pediatric visits in which metoclopramide was mentioned (Table 2). "Feeding problems newborn" diagnosis (ICD-9 code 779.3) was ranked the 3rd in that population in 2004, accounting for less than 5% of the total pediatric visits in which metoclopramide was mentioned during the five-year period from 2000-2004 .

In younger adults aged 17-34 years, while "esophagitis" diagnosis (ICD-9 code 530.1) was ranked the top diagnosis for metoclopramide mentions in the last five-year period from 2000-2004, it accounted on average for only one-fifth of metoclopramide mentions during that period. It should be noted however, that in the five years before 2000, "esophagitis" diagnosis accounted for less than 10% of metoclopramide mentions, with the exception of year 1996, during which esophagitis" diagnosis accounted about 20% of metoclopramide mentions. Thus, "esophagitis" diagnosis, as a reason for use of metoclopramide, seems to be relatively increasing since 2000 in that age group.

In older adults aged 35-64 years as well as in the elderly (aged 65 years and older) "esophagitis" diagnosis (ICD-9 code 530.1) was ranked the top diagnosis for visits during 2000-2004, in which metoclopramide was mentioned, accounting for over 30% of metoclopramide mentions each of these age groups. This diagnosis seems to have increased compared to previous years (1995-1999), during which it accounted for only about 20% of the metoclopramide mentions.

Table 2. Top 5 Diagnoses Associated with Mentions of Metoclopramide During Office-Based Physician Visits by Age Groups, IMS Health, National Disease and Therapeutic Index™, 2000 – 2004

	Drug Uses (%)				
	2000	2001	2002	2003	2004
Diagnoses	**(n=1,549,000)**	**(n=1,715,000)**	**(n=1,559,000)**	**(n=1,527,000)**	**(n=1,480,000)**
Age 0-16	25.5	25.4	**29.1**	**25.0**	**30.9**
530.1 ESOPHAGITIS	75.1	73.3	75.3	85.2	64.9
008.8 OTHER ORGANISM NOT CLASS	---	---	---	0.3	7.0
779.3 FEEDING PROBLEMS NEWBORN	4.5	4.2	2.4	---	4.9
536.8 DYSPEPSIA+DIS FUNCT STOM	0.6	---	---	2.2	4.6
009.1 COLITIS, ENTERITIS, GASTROENTERITIS OF PRESUMED INFECTIOUS ORIGIN	0.5	0.4	3.3	2.8	4.2
Other Diagnoses*	19.4	22.1	19.0	9.5	14.4
Age 17-34	8.4	10.1	**7.5**	**11.0**	**11.0**
530.1 ESOPHAGITIS	21.5	21.5	18.8	28.6	14.1
643.0 MILD HYPEREMESIS GRAVID	3.6	1.7	3.7	6.3	10.8
009.1 COLITIS, ENTERITIS, GASTROENTERITIS OF PRESUMED INFECTIOUS ORIGIN	---	---	---	13.8	9.2
V67.0 POST SURGERY EXAM	5.5	8.3	10.3	5.5	7.0
346.9 MIGRAINE UNSPECIFIED	3.2	5.5	1.4	---	6.9
Other Diagnoses*	66.1	63.1	65.7	45.8	52.1
Age 35-64	36.6	38.5	**36.8**	**38.8**	**32.0**
530.1 ESOPHAGITIS	35.3	36.6	40.8	38.6	34.0
V67.0 POST SURGERY EXAM	9.3	8.1	13.3	6.3	9.0
352.2 OTH DIS GLOSSPHAR NERV	6.3	3.1	3.1	2.5	8.2
787.0 NAUSEA AND VOMITING	7.7	7.6	8.9	2.7	5.1
009.1 COLITIS, ENTERITIS, GASTROENTERITIS OF PRESUMED INFECTIOUS ORIGIN	2.3	1.9	1.2	2.5	4.2
Other Diagnoses*	39.2	42.7	32.7	47.3	39.5
Age 65+	26.2	22.9	**22.7**	**20.7**	**21.1**
530.1 ESOPHAGITIS	32.0	32.5	30.2	34.8	35.2
535.5 UNSP GASTRITIS+GASTRODUO	1.8	0.7	5.9	---	8.8
V67.0 POST SURGERY EXAM	10.8	7.5	6.1	9.3	8.6
789.0 ABDOMINAL PAIN	3.7	8.9	8.2	6.0	6.4
352.2 OTH DIS GLOSSPHAR NERV	3.9	1.8	5.1	4.3	3.8
Other Diagnoses*	47.8	48.5	44.5	45.5	37.2
Unspecified Age	3.3	3.1	**3.9**	**4.4**	**5.0**
530.1 ESOPHAGITIS	40.8	32.1	73.8	41.5	46.9
560.1 PARALYTIC ILEUS	---	---	---	---	12.0
756.7 ANOMALIES ABDOMINAL WALL	---	---	---	---	6.1
536.8 DYSPEPSIA+DIS FUNCT STOM	---	8.2	---	---	5.1
787.0 NAUSEA AND VOMITING	---	4.7	4.4	6.0	5.0
Other Diagnoses*	59.2	55.1	21.9	52.5	25

* Includes diagnoses which are about 15% or less of the total metoclopramide mentions

Physician Specialty

During 2004, internal medicine was the most frequent prescribing specialty, accounting for over 1.2 million (22%) dispensed prescriptions for metoclopramide, followed by family practice (18%), gastroenterology (13%), osteopathic medicine (8%) and pediatric practice (5%) (Figure 5). Together, these specialties accounted for two-thirds of the dispensed prescriptions for metoclopramide during 2004. In general, prescribing patterns for this product showed no change across provider specialties from year 2000-2004 (data not shown).

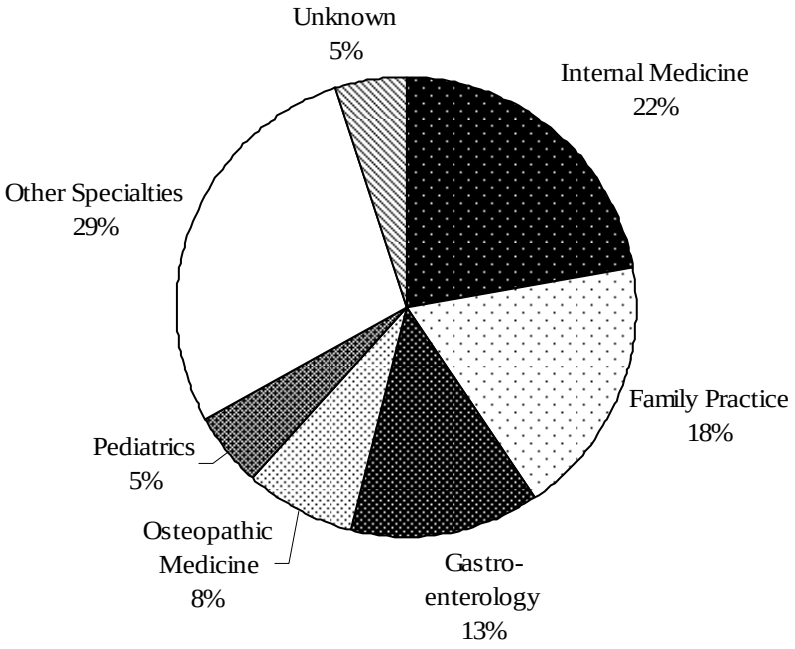

Figure 5. : Distribution of Total Number of Prescriptions Dispensed for Metoclopramide by Physician Specialty, IMS Health, National Prescription Audit *Plus*™, 2004*

IMS Health, National Prescription Audit *Plus*™, Year 2004, Extracted March 2005.
Original file:

* Excluding Long-Term Care and Mail Order Pharmacies

I. Duration of Therapy for Metoclopramide Tablets

A. Characteristics of the Study Population

Over the three-year period from January 1, 2002 through December 31, 2004, there were 572,205 prescription claims for metoclopramide tablets for 200,907 patients who were continuously eligible in the Caremark PBM system during that time period. The characteristics of the study population are shown in Table 3. The mean age of the study population at first prescription was 58 years old (standard deviation (SD) =17.9). Prescriptions claims for metoclopramide were almost exclusively filled by adults and 50% of the claims were filled by persons aged 35-64 years. About two-third of the claims were filled by females and only one-third by males. Approximately 50% of the claims were filled in pharmacies located in the southern region in the U.S.

Table 3. Demographic Characteristics of the Study Population with Prescription Claim for Metoclopramide tablets in Caremark PBM, Caremark's Dimension Rx, 2002-2004

Characteristics	N (Individuals) (Total = 200,907)	%
Age (years)		
1-16	3,399	1.7
17-34	19,166	9.5
35-64	101,083	50.3
65 years or older	77,259	38.5
Gender		
Female	134,918	67.2
Male	65,989	32.9
Region*		
Northeast	26,612	13.3
Midwest	40,940	20.4
South	98,263	49.0
West	32,730	16.3
Other**	2,150	1.1

* 212 individuals are missing information on state
** Other regions include Puerto Rico, Virgin Islands, Northern Mariana Islands, and Guam.
Caremark Dimension Rx™, CD-Rom extracted April 2005

B. Duration of Metoclopramide Use

The average number of prescriptions for metoclopramide per patient was 2.8 (SD=4.7) and ranged from one prescription claim up to a total of 78 prescription claims per patient. Two-thirds of patients (66%) had only one paid prescription claim for metoclopramide. The average days' supply for a prescription claim was 29 days (SD=22.7; range: 1-816 days). The number of episodes ranged from 1 to 20 episodes and about 78% of the study population had only one episode of therapy over the three year period. The average duration of the longest episode for metoclopramide use was 61 days (SD=143.3) and ranged from 1 day to over 2000 days, and thus, could have gone beyond the period of observation. The length of the longest episode of therapy for most patients (87%) varied from 1 to 90 days, yet about 13% of the patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days (Table 4).

Table 4. Duration of the Longest Episode with Metoclopramide Tablets in Caremark PBM, Caremark's Dimension Rx, 2002-2004

Duration of the longest episode*	N (Total =200,907)	%
1-90 days	**175,202**	**87.2**
1-30 days	148,128	73.7
31-60 days	17,369	8.7
61-90 days	9,705	4.8
91 days and over	**25,705**	**12.8**
91-120 days	5,049	2.5
121-180 days	5,857	2.9
181 days and over	14,799	7.4

* calculated for each individual by summing up the total days' supply for each episode. The time lag between the claims was not taken into account in calculating duration of episode of therapy.

During the three-year study period, the average cumulative therapy with metoclopramide was 83 days (SD=179.0) and ranged from 1 day to a total of 2200 days, which was beyond the period of observation. For the majority of the patients in the study (68%), the length of cumulative therapy for metoclopramide was 1 to 30 days (Figure 6). A cumulative therapy period for metoclopramide longer than 90 days was recorded for almost 20% of the patients. As the total cumulative therapy for metoclopramide increased, the frequency of patients decreased; a decrease from 10% of patients treated for 31-60 days to 5% treated for up to 6 months. Yet, the frequency of patients, who had cumulative therapy for metoclopramide for more than 6 months, was over 10%.

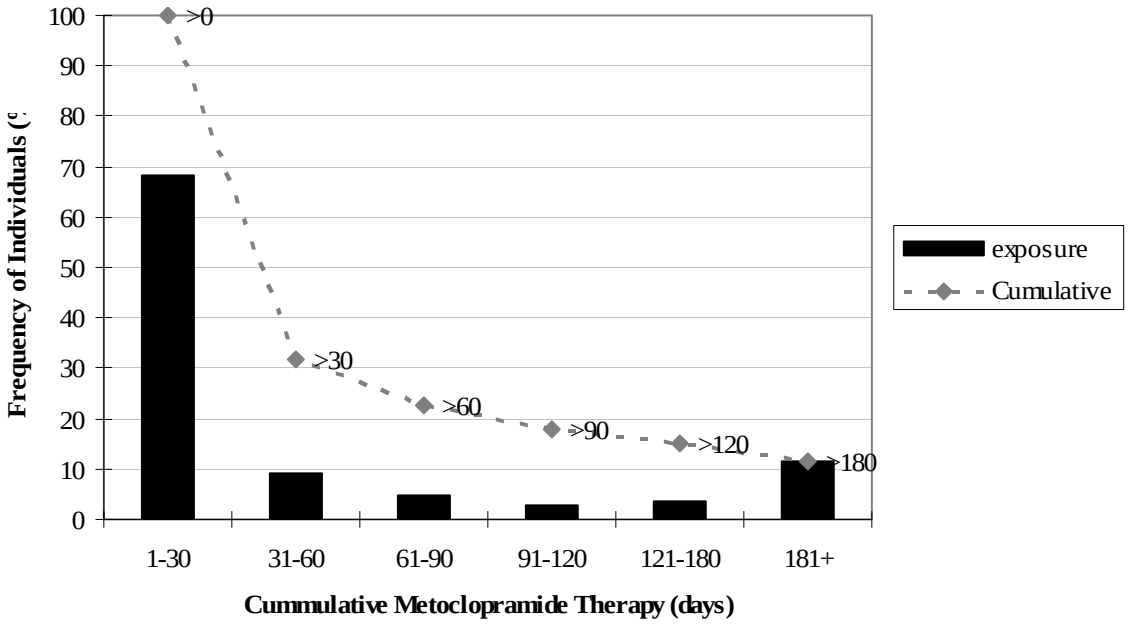

Figure 6. Distribution of Patients by Cumulative Metoclopramide Exposure, Caremark's Dimension Rx, 2002-2004
*Bars add up to 100%; dotted line represents a distribution of cumulative therapy longer than the values noted

Sensitivity Analyses

- *Redefining episode of therapy as no more than a 10-day lag between the dispensing date of a new prescription and the ending date of the preceding prescription.*

The average duration of the longest episode for metoclopramide use was 48 days (SD=112.2). About 10% of the patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days.

- *Excluding individuals with more than 100 days' supply.*

The number of individuals with more than 100 days' supply was 562. After excluding these individuals and all their associated claims, the average duration of the longest episode for metoclopramide use was 60 days (SD=112.2). About 12.6% of the patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days. The average cumulative therapy was 81 days (SD=175.3) and the frequency of patients, who had cumulative therapy for metoclopramide for more than 6 months, was 11%.

- *Redefining the total duration of episode of therapy by adding the time lag between prescription claims.*

The average duration of the longest episode for metoclopramide use was 68 days (SD=158.4). About 15% of the patients appeared to have received prescriptions for metoclopramide for a period longer than 90 days.

DISCUSSION

The increase in the number of prescriptions dispensed for metoclopramide (following the withdrawal of cisapride from the market in 2000) along with the longer than recommended duration of use found in this study was substantial. These results suggest that even with metoclopramide label restrictions on the duration of use and with its well-recognized adverse events, particularly extrapyramidal movement disorders, physicians as well as patients did not follow the labeled recommendation on the duration of therapy. These results may further suggest that a similar label recommendation for a new combination product that contains metoclopramide is not likely to be followed, especially if the product contains naproxen, which is frequently used without restriction on duration of use.

Results from this study are supported by previous finding reported in the literature. An increase in metoclopramide use during the six-month period after the withdrawn of cisapride from the market was observed.[11] This increase was mild and not proportional to the substantial decline observed in cisaprade use, suggesting that cisapride was not available on the market and prescribers responded soon to the market change by seeking substitutions. Nonetheless, this market shift toward an increase in metoclopramide use has potential clinical implications on the incidence of adverse drug reactions, especially when the risk of adverse reactions increases with duration of treatment and cumulative dose. Shaffer et al. has recently reported a series of 87 cases of metoclopramide-associated tardive dyskinesia extracted from FDA's AERS database with remarkably long duration of use (mean=753±951 days).[6] Our data also support a prolonged duration of use (more than 90 days) in over 10% of individuals using metoclopramide, predisposing them to an increased risk of adverse reactions.

Our sensitivity analyses did not substantially change our estimates of duration of the longest episode, duration of cumulative therapy, or the proportion of patients taking metoclopramide for more than 90 days.

It is noteworthy that short duration of therapy for individuals who were taking the drug in the beginning or at the end of the observation period could derive from the boundaries of the study period, as patients could have started an episode of therapy prior to the beginning of the observation period or concluded it after the end of the observation period. On the other hand, episodes with prolonged duration of therapy could also result from errors in the data recorded for days' supply. It should be noted that the operational definition used to define duration of therapy could also account for such extreme measurements. The duration of each episode of therapy was calculated for each episode by summing up the total days' supply from claims that constituted that episode, regardless of the filled date. We found, however, that a small number of metoclopramide claims were filled on the same day, which might suggest that patients were taking a higher dose rather than using the drug for prolonged period. The number of such claims was small (388 in a dataset of 572,205, < 0.1%) and thus unlikely to substantially change our estimates.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. The data, however, do not include historical demographic information, such as age and gender and do not cover all prescriber specialties from mail order and long-term care channels. NDTI™ data, on the other hand, provide estimates of patient demographics and indications for use of medicinal products in the U.S. Yet due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly in sub-categories when use has low prevalence.

Caremark's Dimension Rx™ data derive from a large PBM and may not be nationally representative as patterns across populations may depend on prescription drug coverage. Yet, its large sample size provides a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Nonetheless, these results should be interpreted with caution. For example, the elderly are known to be underrepresented in databases dependent upon prescription drug coverage.

While not comparable to each other in terms of generalizability, we found differences in the proportion of pediatric use for metoclopramide between NDTI™ (30%) and Caremark's Dimension Rx™ (<2%). Some of this difference can derive from the fact that NDTI™ captures drug mentions, which includes but is not limited to written prescriptions during office visits, while Caremark captures prescriptions filled. Another source that could account for this difference is the dosage form of metoclopramide in these databases; NDTI™ included all oral forms, while our analysis of Caremark dataset was limited to metoclopramide tablets only. It is also noteworthy that the majority of the metoclopramide mentions during pediatric visits in NDTI™ dataset were for children up to 3 years old and mentions for this age group consisted of about one-fifth or one-fourth of all metoclopramide mentions during office visits from 2002-2004. In the Caremark dataset, infants under one year of age were excluded but could have accounted for a significant proportion of metoclopramide claims excluded, as use could be higher in the first year of life. Finally, the continuous enrollment eligibility criteria for the entire study population could probably account for much of the difference, as large proportions of young children would not meet the eligibility criteria and would therefore have been excluded from the Caremark analysis.

CONCLUSION

Results from this study indicate that the number of prescriptions dispensed for metoclopramide, which was declining from 1995 to 1999, has more than tripled in the five-year period following the withdrawal of cisapride from the market in March 2000. In addition to this increase in the U.S. in recent years, data from an insured population source showed that over 10% (10-15%) of metoclopramide users had claims suggestive of use for a period longer than the three months recommended in the label. Moreover, total cumulative therapy with metoclopramide longer than 6 months was found in about 10% of the study population.

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