Mortality, Outcomes, and Healthcare Costs in T2DM Patients at Risk for Cardiovascular Disease

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ABSTRACT

OBJECTIVES: To evaluate cardiovascular outcomes and economic burden among type 2 diabetes mellitus (T2DM) patients at high risk for adverse cardiovascular events in a managed care setting.

STUDY DESIGN: Retrospective cohort study.

METHODS: Patients 40 years and older diagnosed with T2DM between January 1, 2007, and April 30, 2011, were identified with medical and pharmacy claims in a large US managed care database and followed for up to 5 years. T2DM diagnoses were based on 2 medical claims with diabetes-related *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, or on 1 medical claim plus 1 pharmacy claim for diabetic medication. Patients with established cardiovascular disease (CVD) were classified as the secondary prevention cohort while those without established CVD but with CVD risk factors constituted the primary prevention cohort. Outcomes of myocardial infarction (MI), stroke, and death were evaluated using Kaplan-Meier survival analysis.

RESULTS: Of the overall study population (N = 368,581), the secondary prevention cohort consisted of 177,140 patients, and the primary prevention cohort had 191,441 patients. Fifty-seven percent of patients were male and the mean age was 67.1 years. Both cohorts had high rates of mortality, stroke, and hospitalization for MI during follow-up. Mortality rates were 20% and 7% in the secondary and primary prevention groups, respectively, after 4 years of follow-up. Healthcare costs for the overall study population were $12,962 per patient-year of follow-up.

CONCLUSIONS: T2DM patients with established CVD or CVD risk factors are at significant risk for mortality and CVD events. They incur high healthcare utilization and costs, driven by inpatient hospitalizations and outpatient visits.

Diabetes mellitus affects an estimated 25.8 million adults in the United States, and prevalence is expected to more than double by 2050, with the largest increases in older age groups.[1,2] Type 2 diabetes mellitus (T2DM) accounts for up to 95% of all diagnosed cases of diabetes in adults.[2] The increasing prevalence of T2DM imposes substantial mortality, morbidity, and healthcare cost burdens on society.

Patients with diabetes are at risk for both microvascular and macrovascular complications; macrovascular events (eg, stroke and myocardial infarction [MI]) are the leading cause of death in this population.[2] The risk of stroke and death is 2 to 4 times greater for adults with T2DM than for the general population.[2,3] Diabetes was an underlying or contributing cause of death for more than 230,000 individuals in the United States in 2007.[1] T2DM patients often have comorbid conditions, including hypertension and dyslipidemia, which confer additional risk of cardiovascular (CV) events.[4,5]

The management of T2DM includes the use of insulin and several classes of oral medication along with appropriate diet, more exercise, and other lifestyle changes.[6,7] Antihyperglycemic agents have shown to be effective in controlling blood glucose in the short term and in reducing the risk of the microvascular sequelae of diabetes. Furthermore, a meta-analysis of randomized clinical trials concluded that intensive glycemic control reduces coronary events compared with standard glycemic control, without increasing mortality risks.[8]

The evidence is inconclusive, however, on the ability of specific antihyperglycemic treatments to reduce the risk of major CV events and death in this patient population.[9] Treatment effects appear to vary by drug class. A meta-analysis on the thiazolidinedione drug,

Table 1. Demographics of Study Population

	Total Population (T2DM with CV risk) n = 368,581	Secondary Prevention (established CVD) n = 177,140	Primary Prevention (CV risk, no CVD) n = 191,441
Number of patients	368,581	177,140	191,441
Follow-up, years (mean ± SD)	2.78 ± 1.72	2.73 ± 1.75	2.84 ± 1.7
Age, years (mean ± SD)	67.1 ± 10.5	68.1 ± 12.3	66.2 ± 8.3
Male (%)	57.3	57.1	57.5
Type of health plan (%)[a]			
HMO	21.9	22.5	21.3
PPO	71.1	70.5	71.6
Other commercial[b]	7.1	7.0	7.1
Region (%)[a]			
Northeast	21.1	22.0	20.2
Midwest	34.3	36.5	32.2
South	28.7	26.9	30.3
West	16.0	14.6	17.3

CV indicates cardiovascular; CVD, cardiovascular disease; HMO, health maintenance organization; PPO, preferred provider organization; T2DM, type 2 diabetes mellitus.

[a]Categories may not total 100% due to rounding.

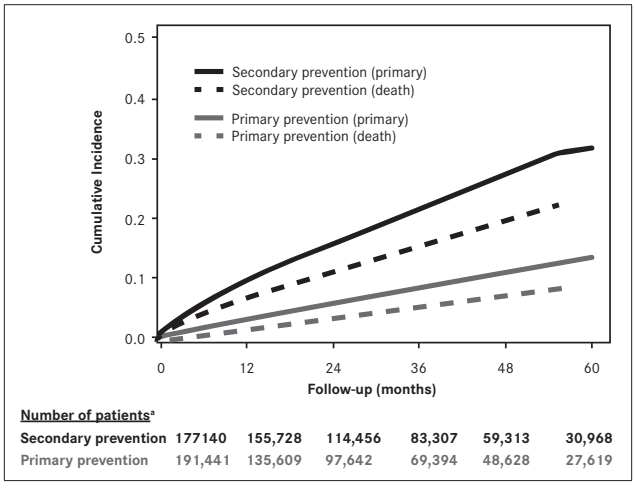
[b]Includes consumer-driven (high-deductible) health plans, health incentive accounts, Medicare (supplemental), and unknown or missing data.

rosiglitazone, raised concerns over increased risk of death from CV causes,[10] and a nationwide observational cohort study suggested increased CV risk with sulfonylureas compared with metformin.[10,11] Such evidentiary variations and knowledge gaps about treatment outcomes indicate an urgent need for rigorous long-term evidence for decision making.[11,12]

A handful of clinical trials—including a few evaluating dipeptidyl peptidase 4 (DPP-4) inhibitors—are under way to assess the efficacy and safety of T2DM treatment interventions on CV end points.[13,14] One prominent study, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) 53, is a phase 4, randomized, double-blind, placebo-controlled trial. With an expected duration of 5 years, the study enrolled 16,500 patients in 25 countries to evaluate the safety of saxagliptin treatment and its effect on CV events in T2DM patients.[13] In an update, which assessed 16,492 patients after a median time of 2.1 years, the authors reported that saxagliptin treatment neither increased nor decreased the rate of ischemic events, although hospitalization and heart failure rates increased. They concluded that even though saxagliptin was associated with better glycemic control, other approaches were needed to reduce CV risk among T2DM patients.[14]

The purpose of the present study was to understand and quantify real-world outcomes for patients with T2DM and high CV risk, and to assess the cost burden of these outcomes in a US-based private payer setting.

Figure 1. Kaplan-Meier Analysis of Primary Outcome Incidence Rates



[a]The number of patients includes patients in the risk set for the primary outcome at the time point of interest.

Methods

Data Source

All study data were queried from the HealthCore Integrated Research Environment (HIRE), a repository of medical and pharmacy claims data on approximately 30 million health plan members (at the time of the study), drawn from 14 geographically dispersed US commercial health plans. Researcher access was limited to de-identified data to ensure patient privacy and confidentiality. Strict measures were observed to ensure full compliance with the Health Insurance Portability and Accountability Act. Study data query dates included the period from January 1, 2007, through April 30, 2012, and to ensure a minimum follow-up time of 12 months for all patients, the study intake period was set at January 1, 2007, through April 30, 2011. The length of follow-up varied for the patients. Mortality data was obtained from the Social Security Death Index (SSDI) and matched with data from the HIRE repository to determine the date of death as applicable. All analyses were conducted under a pre-specified research plan, in accordance with current best practices for retrospective research.[15,16]

Patient Selection

The study population consisted of adults 40 years and older with T2DM, which was defined as having at least 2 claims with an

International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis indicating T2DM (*ICD-9-CM* 250.x0 or 250.x2) or 1 T2DM diagnosis plus a prescription fill for an antidiabetic medication. The index date was defined as the earliest date during the study intake period at which the criteria for T2DM diagnosis were satisfied. The study population was further stratified into 2 cohorts: secondary and primary prevention. The secondary prevention cohort had established CV disease (CVD), defined as a history of MI, ischemic stroke/transient ischemic attack, peripheral vascular disease, unstable angina, congestive heart failure, other coronary heart disease, or revascularization procedures within the 12 months preceding the index date. The primary prevention cohort consisted of patients at risk for CVD and included patients aged 55 years or more (men) or aged 60 years or more (women) who had a diagnosis of hypertension, dyslipidemia, or both. Hypertension and dyslipidemia were each defined as having at least 1 *ICD-9-CM* diagnosis code or at least 2 medication prescription fills for the condition, within the 12 months prior to the index date. Those without established CVD and no CVD risk factors were excluded from the study.

Analyses

The primary outcome was a composite event of all-cause death, stroke, or MI. All-cause deaths, as opposed to cardiovascular-related deaths, were used to measure mortality in this analysis because the actual cause of death is not reported in the SSDI. For stroke and MI, any hospitalization with a primary diagnosis code for stroke or MI and a minimum 1-night stay was defined as an event. The time to first event was captured on a per patient basis and analyzed via Kaplan-Meier analysis. Event rates were calculated over total patient-years of follow up, both for the entire study population and for each risk cohort. Healthcare resource utilization and costs were summarized, and consisted of both plan-paid and patient-paid costs. The Consumer Price Index for medical care, provided by the US Bureau of Labor Statistics, was used to convert prices to 2011 constant US dollars.[17] All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina); descriptive statistics were reported.

Results

Patient Characteristics

Of the more than 21 million enrollees in HIRE between January 1, 2007, and April 30, 2011 (the intake period), more than 1 million met the criteria for T2DM diagnosis. A total of 604,882 T2DM patients aged 40 years or more had continuous health plan enrollment for at least 12 months prior to the index date identified (**Appendix Figure**). Of these patients, 368,581 with either established CVD or CV risk factors were identified and included in the analysis; 236,301 who did not have CVD or CV risk factors were eliminated from the analysis. The 368,581 patients were placed in the secondary prevention (n = 177,140) or primary prevention cohorts (n = 191,441) and were followed from first diagnosis (index date) until loss of eligibility, end of study period, or death.

The purpose of the present study was to understand and quantify real-world outcomes for patients with T2DM and high CV risk, and to assess the cost burden of these outcomes in a US-based private payer setting.

A majority of patients (57.3%) were male; overall, 71.1% received coverage under preferred provider organization health plans. The mean age was 67.1 years for the total study population, and was slightly higher in the secondary prevention cohort despite the application of stricter age requirements for the primary prevention group (**Table 1**). Patients were treated at sites in all regions of the United States, with the largest representation from the midwest and south. More than 80% of the population had dyslipidemia and nearly 90% had hypertension (**Table 2**). A prescription for antidiabetic medication was filled by 43.8% of the sample in the 12 months preceding their index T2DM diagnosis, including metformin (24.5%), sulfonylureas (17.4%), and thiazolidinediones (14.1%). Other medical comorbidities were frequent—particularly among patients in the secondary prevention cohort. Of the conditions utilized to identify the cohort with prior CVD, other coronary heart disease conditions (including atherosclerosis, aortic aneurysm, post MI syndrome, and revascularization procedures, among others) were the most common (66.8%), followed by ischemic stroke/transient ischemic attack (30.5%), congestive heart failure (28.1%), and peripheral vascular disease (26.5%); MI (13.9%) and unstable angina (7.3%) were less common. Nearly half (49.7%) of patients with CVD had a Deyo Charlson Comorbidity Index (DCCI) score of 3 or higher. The DCCI is based on 17 diagnoses, identified by *ICD-9-CM* codes, each with a weight of 1 to 6. The final score is derived from the sum of the weighted values of the comorbidities present; higher scores signify greater comorbidity burden.[18]

Outcomes

Over the follow-up period—which averaged 2.78 years—14.3% of all patients experienced at least 1 of the primary outcome events:

Figure 2. Healthcare Utilization Rates per Person-Year of Follow-up

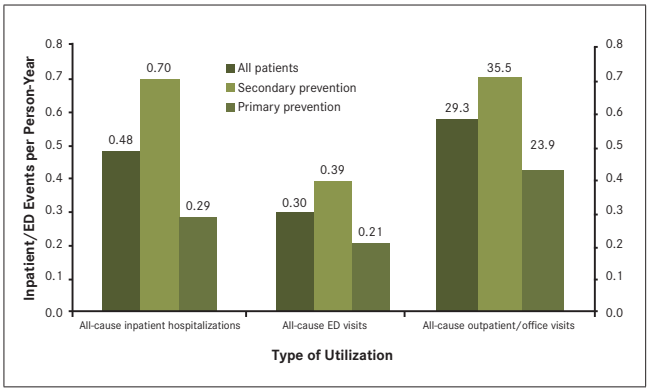


Table 2. Disease Characteristics and Comorbid Conditions at Index Date

	Total population (T2DM with CV risk) n = 368,581	Secondary prevention (established CVD) n = 177,140	Primary prevention (CV risk, no CVD) n = 191,441
Any anti-hyperglycemic medication (%)[a]	43.8	42.0	45.5
Metformin	2.78 ± 1.72	2.73 ± 1.75	27.8
Sulfonylureas	67.1 ± 10.5	68.1 ± 12.3	17.4
Thiazolidinediones	57.3	57.1	15.1
Insulin	21.9	22.5	7.2
Fixed dose combinations	71.1	70.5	5.9
Deyo Charlson Comorbidity Index (DCCI) (mean ± SD)	2.2 ± 2.0	3.0 ± 2.2	1.4 ± 1.3
DCCI score ≥3 (%)	30.8	22.0	13.3
Cardiovascular comorbidities (%)			
Myocardial infarction	6.7	13.9	n/a
Ischemic stroke, TIA, or cerebrovascular disease	14.6	30.5	n/a
Unstable angina	3.5	7.3	n/a
Peripheral vascular disease	12.8	26.5	n/a
Congestive heart failure	13.5	28.1	n/a
Other coronary heart disease	32.1	66.8	n/a
CVD risk factors (%)			
Age risk (men ≥55 y, women ≥60 y)	91.0	81.2	100.0
Dyslipidemia	80.3	80.9	79.7
Other comorbid disease (%)			
Chronic renal dysfunction	12.8	19.3	6.7
Cancer	14.3	16.5	12.2
Gout	4.5	5.4	3.6
COPD	6.0	9.7	2.6
Asthma	7.5	9.8	5.4
Emphysema	2.2	3.6	0.8
Dyspnea and other respiratory abnormalities	21.5	34.2	9.8

CV indicates cardiovascular; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; T2DM, type 2 diabetes mellitus; y, years.

[a]<2% prevalence of GLP-1 agonists, DPP-4 inhibitors, amylin analogues, or meglitinide analogues (not shown).

all-cause death, hospitalization for MI, or hospitalization for stroke. In the secondary prevention cohort, 21.1% of patients had at least 1 event, while 8% of patients in the primary prevention cohort experienced an event. The incidence rate of these events, considering only the first event for each patient, was 53.3 per 1000 patient-years of observation in the overall population; 81.8 per 1000 patient-years in the secondary prevention cohort; and 28.8 per 1000 patient-years in the primary prevention cohort (**Table 3**). The majority of the observed events were deaths from any cause (56.2% of all events—34,961 deaths out of 62,219 total events). Stroke presented a greater risk as a cause of hospitalization than did MI. Kaplan-Meier estimates of the time to first event showed that more than 1 in 4 patients with diabetes and established CVD in this sample could be expected to experience a stroke or MI, or die from any cause, during the 4 years of follow-up (**Figure 1**). Secondary outcomes, including hospitalizations due to other CV causes, were also common, with hospitalizations due to heart failure and revascularization procedures especially prevalent among patients in the secondary prevention cohort (**Table 4**).

Hospitalization rates were 701 and 290 events per 1000 patient-years in the secondary prevention and primary prevention cohorts, respectively (**Figure 2**). The average cost per patient per year among all patients was $12,962 ($16,227 in the secondary and $10,059 in the primary prevention cohorts) (**Figure 3**). Costs per patient-year were driven primarily by inpatient days, outpatient visits, and pharmacy costs in both cohorts.

Discussion

The study cohort—primary prevention plus secondary prevention—represents an older population (mean age 67.1 years) with T2DM, and thus, an elevated risk of stroke, MI, and death. Over the follow-up period, patients in this population experienced high rates of hospitalization and outpatient visits, which contributed to their substantial healthcare costs. Comorbid conditions were prevalent, including chronic renal dysfunction, cancer, and respiratory conditions. All-cause mortality was especially high in the group with established CVD. More than 1 in 4 patients in this subgroup died or were hospitalized for MI or stroke within 4 years after the index date. Event rates in this study are consistent with those in prior studies, which demonstrated substantially higher CV event rates in populations of T2DM patients with CVD compared with those without CVD.[19,20] These findings underscore the importance of treatment options for T2DM patients at elevated risk of CV events.

Other studies of diabetic patients have assessed similar outcomes.

Table 3. Primary Outcome Events During Follow-up Period

	Total population (T2DM with CV risk) n = 368,581	Secondary prevention (established CVD) n = 177,140	Primary prevention (CV risk, no CVD) n = 191,441
Patient-years of observation (primary outcome)[a]	987,840	457,250	530,589
Patients with an event (%)	14.3	21.1	8.0
Incidence rates per 1000 patient years[b]			
Primary outcome: death (any reason) or hospitalization due to MI or stroke	53.3	81.8	28.8
Death (all-cause)	34.1	53.6	16.7
MI hospitalization	9.1	13.1	5.6
Stroke hospitalization	14.4	20.9	8.7
Incidence rates for primary outcome, by risk and age strata[c]			
≥65 y	77.8	111.7	42.9
Hypertension subgroup	55.5	83.5	30.4
Dyslipidemia subgroup	46.8	71.2	25.0

CV indicates cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; y, years.

[a]Follow-up stopped at first event. Patients without an event were censored at the end of health plan enrollment or the end of the study period, whichever came first.

[b]Calculated as the number of patients having at least 1 event divided by the total number of patient-years of observation, multiplied by 1000.

[c]In the primary prevention cohort, patients were required to have an age risk factor (55 years or older for men, 60 years or older for women) and either hypertension or dyslipidemia in order to qualify for inclusion in the analysis.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial also examined rates of MI, stroke, and death (due to any cause and cardiovascular-related) in T2DM patients with high CVD risk.[21,22] The ACCORD trial studied the effect of different therapeutic interventions (including lipid-lowering and blood-pressure–lowering medications) on each of these outcomes, while our study did not require any type of medical intervention. Outcomes in the ACCORD were less common than what was found in the current study, possibly due to therapeutic intervention, with event rates per 1000 person years ranging from 11.9 to 16.1, 11.3 to 14.4, and 3.0 to 4.7 for all-cause mortality, nonfatal MI, and nonfatal stroke, respectively.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial also studied cardiovascular outcomes within a T2DM patient population.[23,24] All patients in the ADVANCE trial were assigned to a therapeutic group for intensive blood glucose control or standard blood glucose control. Of the patients in the standard control group, 2.8% had a nonfatal MI, 3.8% had a nonfatal stroke, and 9.6% died from any cause. Those results were similar to the findings in this study—2.5% with MI, 3.9% with stroke, and 9.5% all-cause death—although median follow-up time in ADVANCE was roughly twice as long (5 years vs 2.6 years in our study).

The use of a large real-world existing data resource allowed for the reporting of timely estimates of event rates and healthcare costs in this population, with a search cutoff date of April 2012. In addition, this study included patients in a real-world setting, without having to restrict patients due to clinical trial criteria or requiring therapeutic intervention.

Limitations

The limitations of the study include reliance on medical claims data, which lack clinical detail and are subject to potential coding, billing, and recording errors, as well as other inconsistencies. Claims databases also include only patients with specific healthcare coverage—in this case, coverage provided by private commercial health plans. Notably, patients without health insurance and a substantial portion of those who are covered under federal plans (Medicare or Medicaid)

Figure 3. Healthcare Utilization Rates per Person-Year of Follow-up

All costs reported in 2011 US dollars. Data weighted according to patient follow-up time (in years).

Table 4. Secondary Outcome Events During Follow-up Period: Incidence Rates per 1000 Patient-Years[a]

	Total population (T2DM with CV risk) n = 368,581	Secondary prevention (established CVD) n = 177,140	Primary prevention (CV risk, no CVD) n = 191,441
Total patient-years of observation[b]	1,026,415	483,068	543,346
Incidence rates per 1000 patient-years[a]			
CHF hospitalization			
Coronary revascularization	53.3	81.8	28.8
Death (all-cause)	34.1	53.6	16.7
MI hospitalization	9.1	13.1	5.6
Stroke hospitalization	14.4	20.9	8.7
Incidence rates for primary outcome, by risk and age strata[c]			
≥65 y	77.8	111.7	42.9
Hypertension subgroup	55.5	83.5	30.4
Dyslipidemia subgroup	46.8	71.2	25.0
Gout	4.5	5.4	3.6
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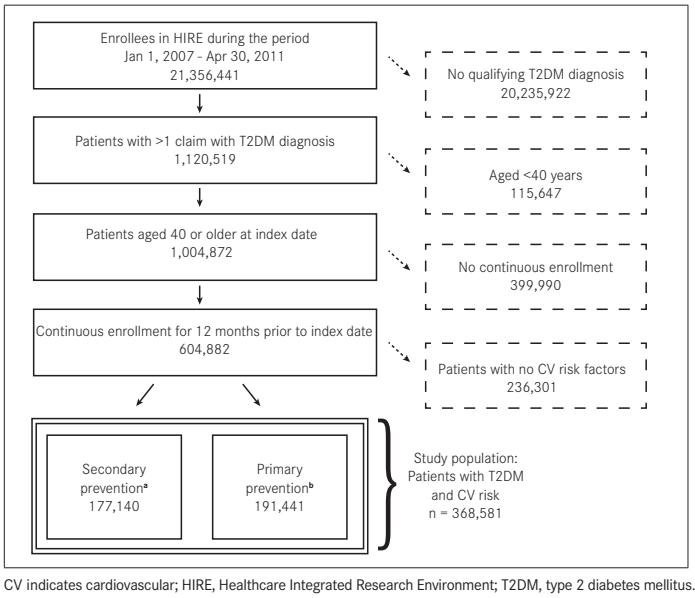
[a]Follow-up stopped at first event. Patients without an event were censored at the end of health plan enrollment or the end of the study period, whichever came first.

[b]Calculated as the number of patients having at least 1 event divided by the total number of patient-years of observation, multiplied by 1000.

[c]In the primary prevention cohort, patients were required to have an age risk factor (55 years or older for men, 60 years or older for women) and either hypertension or dyslipidemia in order to qualify for inclusion in the analysis.

Appendix Figure. Patient Selection



CV indicates cardiovascular; HIRE, Healthcare Integrated Research Environment; T2DM, type 2 diabetes mellitus.

[a]Prior stroke, MI, peripheral vascular disease, heart failure, other coronary heart disease, or revascularization in the 12 month pre-index period.

[b]Age 55 or older (men) or 60 or older (women), plus dyslipidemjia and/or hypertension diagnosis or medication in the 12-month pre-index period.

are not part of the analyzed population; therefore, the ability to generalize these results to the entire US population may be limited. The requirement for continuous medical and pharmacy coverage prior to the index date, which resulted in exclusion of one-third of otherwise eligible patients, could have introduced further bias. In addition, due to the lack of availability of certain clinical data, inclusion criteria and outcome definitions commonly used in clinical trials were not able to be exactly replicated. Specifically, blood glucose, lipids, and blood pressure levels, and the use of smoking status as a risk factor for CVD were not used; nor was there any requirement that patients have a minimum life expectancy at time of enrollment. Ideally, we would also have data on CV-related death, however, the SSDI does not specify the cause of death, and thus, only all-cause death was analyzed in this study.

Conclusions

Analysis of this large US database indicates that T2DM patients with either CV risk factors or previous CV disease experience high morbidity and mortality and incur substantial healthcare-related costs. Treatment goals that focus on glucose control and management of CV risk factors may prevent future CV events, thereby reducing costs to the healthcare system.

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Author Disclosures: *Dr Tunceli and Mssrs Kern and Wu are employees of HealthCore, Inc, which received funding from AstraZeneca for this work. Ms DeVore was an employee of AstraZeneca during the time the study was conducted and the manuscript was written. Drs Hirshberg and Kim are employees of AstraZeneca.*

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INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension

INDICATION

Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.

- **Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.**

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

FOR THE **TREATMENT OF SCHIZOPHRENIA**

An option that may help your members delay relapse

Abilify Maintena® (aripiprazole) significantly delayed the time to relapse* vs placebo (*P*<0.0001)

Visit AbilifyMaintena.com for product information and Formkit.com for formulary information.

*In a Phase III, 52-week, double-blind, randomized-withdrawal clinical trial; Abilify Maintena (n=269) vs placebo (n=134).

IMPORTANT SAFETY INFORMATION *(continued)*

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including Abilify Maintena. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Continued on next page.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

400MG

Abilify Maintena®

(aripiprazole) for extended release injectable suspension

IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension *(continued)*

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).
- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension. Abilify Maintena should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions: Abilify Maintena should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Abilify Maintena may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain Abilify Maintena does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with Abilify Maintena; use caution in patients at risk for aspiration pneumonia.

Alcohol: Advise patients to avoid alcohol while taking Abilify Maintena.

Concomitant Medication: Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the Abilify Maintena dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

Most commonly observed adverse reaction: The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs placebo, respectively, was:

- Akathisia (8% vs 4%) in adult patients with schizophrenia.

Injection Site Reactions: In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena-treated patients.

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on adjacent pages.

ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details, please see *Full Prescribing Information and Medication Guide*.)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
- ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis

INDICATIONS AND USAGE: ABILIFY MAINTENA (aripiprazole) is indicated for the treatment of schizophrenia. Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.

CONTRAINDICATIONS: ABILIFY MAINTENA is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole.

WARNINGS AND PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, in oral aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with oral aripiprazole. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY MAINTENA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with ABILIFY MAINTENA drug discontinuation should be considered. However, some patients may require treatment with ABILIFY MAINTENA despite the presence of the syndrome.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving ABILIFY MAINTENA as well.

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes), who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

  In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 1 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 1: Changes in Fasting Glucose From Placebo-controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

  There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

  Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 2: Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	Aripiprazole	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/ nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

  Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

Table 3: Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	Aripiprazole	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	Aripiprazole	719	16 (2.2)
		Placebo	598	16 (2.7)

[a]4-6 weeks' duration. [b]3 weeks' duration.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with ABILIFY MAINTENA during the stabilization phase, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) was 0.2% (1/575).

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including oral aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC counts until recovery.

Seizures: As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS: The following adverse reactions are discussed in more detail in other sections of the labeling in the *Full Prescribing Information:*

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.9)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety Database of ABILIFY MAINTENA and Oral Aripiprazole: Aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications, and who had approximately 8,578 patient-years of exposure to oral aripiprazole. A total of 3,901 patients were treated with oral aripiprazole for at least 180 days, 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment for at least 720 days.

ABILIFY MAINTENA 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult patients in clinical trials in schizophrenia, with approximately 1,281 patient-years of exposure to ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 630 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and open-label studies. The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. Therefore, most of the safety data presented below are derived from trials with the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections under double-blind conditions, the incidence of adverse reactions was similar between the two treatment groups.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole: *Adverse Reactions Associated with Discontinuation of Oral Aripiprazole:* Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the incidence of discontinuation due to adverse reactions was 7% in oral aripiprazole-treated and 9% in placebo-treated patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions of Oral Aripiprazole: Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the only commonly observed adverse reaction associated with the use of oral aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

Less Common Adverse Reactions in Adults Treated with Oral Aripiprazole: Table 4 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with oral aripiprazole (doses ≥2 mg/ day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction[a]	
System Organ Class Preferred Term	**Oral Aripiprazole (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Dose-Related Adverse Reactions of Oral Aripiprazole: Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Injection Site Reactions of ABILIFY MAINTENA: In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the first to the last injection in the open-label, stabilization phase (6.1 to 4.9).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent for 74%-96% of subjects following the first injection and 77%-96% of subjects following the last injection.

Extrapyramidal Symptoms of Oral Aripiprazole: In short-term, placebo-controlled trials in schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, –0.05).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias) did not show a difference between aripiprazole and placebo.

Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials of Oral Aripiprazole: The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for oral aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (40/859) for oral aripiprazole.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6),* or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: ≥1/1000 patients and <1/100 patients - thrombocytopenia; Cardiac Disorders: ≥1/1000 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia; <1/1000 patients - atrial flutter, supraventricular tachycardia, ventricular tachycardia; *Eye Disorders:* ≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia; *Gastrointestinal Disorders:* ≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; <1/1000 patients - pancreatitis; *General Disorders and Administration Site Conditions:* ≥1/100 patients - asthenia, peripheral edema, chest pain; ≥1/1000 patients and <1/100 patients - face edema, angioedema; <1/1000 patients - hypothermia; *Hepatobiliary Disorders:* <1/1000 patients - hepatitis, jaundice; *Immune System Disorders:* ≥1/1000 patients and <1/100 patients - hypersensitivity; *Injury, Poisoning, and Procedural Complications:* ≥1/100 patients - fall; <1/1000 patients - heat stroke; Investigations: ≥1/1000 patients and <1/100 patients - blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased; <1/1000 patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased; *Metabolism and Nutrition Disorders:* ≥1/1000 patients and <1/100 patients - anorexia, hyponatremia, hypoglycemia, polydipsia; <1/1000 patients - diabetic ketoacidosis; *Musculoskeletal and Connective Tissue Disorders:* ≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; <1/1000 patients - rhabdomyolysis; *Nervous System Disorders:* ≥1/100 patients - coordination abnormal; ≥1/1000 patients and <1/100 patients - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; <1/1000 patients - choreoathetosis; *Psychiatric Disorders:* ≥1/100 patients - suicidal ideation; ≥1/1000 patients and <1/100 patients - loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; <1/1000 patients - catatonia, sleepwalking; *Renal and Urinary Disorders:* ≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; <1/1000 patients - gynecomastia, priapism; *Respiratory, Thoracic, and Mediastinal Disorders:* ≥1/100 patients - nasal congestion, dyspnea; *Skin and Subcutaneous Tissue Disorders:* ≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥1/1000 patients and <1/100 patients - pruritus, photosensitivity reaction, alopecia, urticaria.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm).

DRUG INTERACTIONS: Carbamazepine or Other CYP3A4 Inducers: Concomitant use of ABILIFY MAINTENA with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days *[see Indications and Usage, Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].*

Ketoconazole or Other Strong CYP3A4 Inhibitors: Concomitant use of ABILIFY MAINTENA with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

Quinidine or Other Strong CYP2D6 Inhibitors: Concomitant use of ABILIFY MAINTENA with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of quinidine or other CYP2D6 inhibitors with ABILIFY MAINTENA does not require a dose adjustment.

CNS Depressants: Given the CNS depressant effects of aripiprazole, use caution when ABILIFY MAINTENA is taken in combination with other centrally-acting drugs or alcohol.

Anti-Hypertensive Agents: Due to its α_1-adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category C: Risk Summary:* Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1-10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m^2 body surface area. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data: Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/ kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m^2 body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

Nursing Mothers: Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients <18 years of age have not been evaluated.

Geriatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients >60 years of age have not been evaluated. In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment of ABILIFY MAINTENA is recommended for elderly patients *[see also Boxed Warning and Warnings and Precautions (5.1)].*

CYP2D6 Poor Metabolizers: Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].*

OVERDOSAGE: Human Experience: The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage: In case of overdosage, call the Poison Control Center immediately at 1-800-222-1222.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ABILIFY MAINTENA.

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