

# Meaningful Use Gets Mixed Reviews From Users

BY ALICIA AULT

Many physicians are frustrated and confused by the meaningful use criteria that spell out how they can receive incentive payments from Medicare and Medicaid for their use of electronic health records.

With that uncertainty, physicians are not jumping in with both feet to participate in the incentive program, even if they have purchased EHR systems. The Medical Group Management Association (MGMA), in an April survey of its members, found that 80% of those who had adopted an EHR system intended to participate. But at that time, only 14% said they were able to meet all the criteria.

The American Medical Association held a special session on meaningful use at its House of Delegates meeting in June. When Dr. Michael L. Hodgkins, AMA chief medical information officer, asked how many physicians were confused about what was expected of them, more than half raised their hands.

Physicians in smaller practices are especially challenged, Dr. Hodgkins said, citing data that some 300,000 doctors are in practices of 10 or fewer physicians. Among those, fewer than 15% have implemented an EHR system, and most are not yet capable of meeting the meaningful use criteria.

According to Dr. Hodgkins, there are many obstacles to meeting meaningful use, including selecting from the more than 400 EHR products certified by the federal Office of the National Coordinator (ONC) for Health Information Technology, part of the Health and Human Services department.

Another problem: "Aggressive" timelines set by the government, according to

Dr. Steve Waldren, director of the Center for Health Information Technology at the American Academy of Family Physicians (AAFP). He says it takes 6-18 months from purchase to active meaningful use of a system.

It's been a tough road, he said. Physicians who don't have EHRs or who have just gotten on board are struggling to get them operational and to achieve meaningful use. Those who have owned systems for awhile may face upgrades to meet the meaningful use criteria.

Meanwhile, there's the system's financial cost, its training and maintenance issues, and workflow changes once a system is in place.

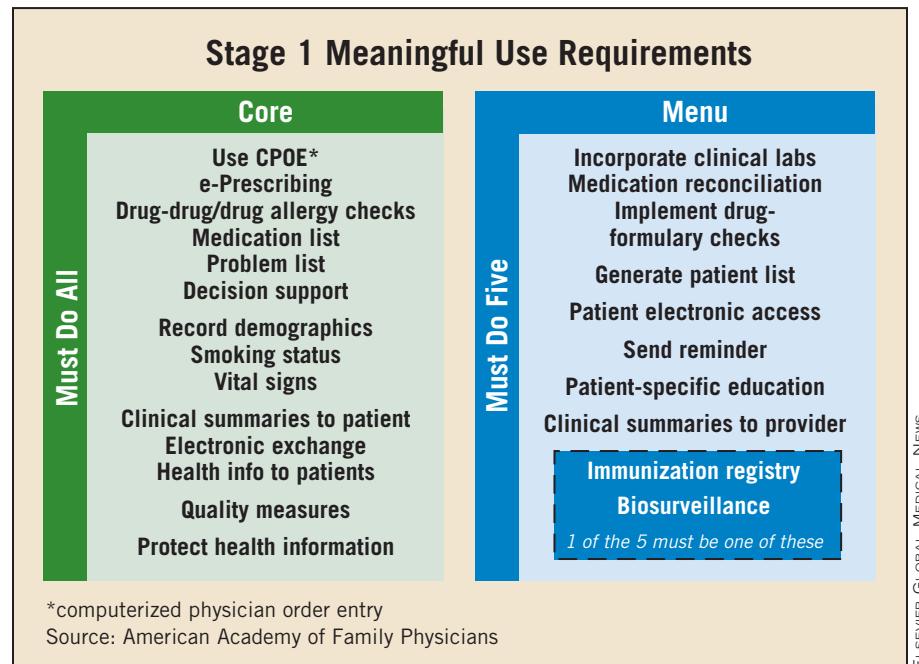
## The Long-Time User

Some physicians aren't in a panic about the impending deadlines. Dr. Michael Mirro of Ft. Wayne (Ind.) Cardiology, a 24-physician group, said his practice has been using health IT since 1996.

"We knew that we had to ultimately modernize our practice," Dr. Mirro said in an interview. Their current system has improved efficiency and quality, and has "supported a higher level of coding and reimbursement."

The system has "pretty much complete functionality," said Dr. Mirro. It provides the EHR, offers e-prescribing and decision-support tools, and can be used for direct quality reporting to the American College of Cardiology's PINNACLE registry.

The system is Web based, which reduces maintenance costs and IT headaches. The practice does not own the servers; it has local computers that interact with the vendor's servers and software. The system is certified by the Certification Commission for Health Information Technology and was updated



ed to ensure that the practice would meet the meaningful use criteria. One helpful tool, according to Dr. Mirro: A meaningful use "meter" that tells the physicians how well they are meeting the goals.

Ft. Wayne Cardiology has already at-tested to the government that it was a meaningful user and has received the maximum \$18,000 per physician incentive for 2011, Dr. Mirro said.

The annual cost is about \$2,000 per physician per year. That's low, said Dr. Mirro, because his practice is owned by a hospital. The system is already ahead of the curve, as it already incorporates a patient Web portal (a stage 2 goal).

He said that he is sympathetic to physicians who are just getting started. "Any time you adopt technology at the point of care, it's going to require a change in workflow," he said. That was definitely

the case at Ft. Wayne Cardiology.

Dr. Mirro said that physicians looking to buy or expand their health IT should talk with one of the 60 regional extension centers established by the ONC. These centers have been charged to help rural and primary care physicians especially. They offer vendor recommendations, practice audits, and other advice for free.

## A Model for Her Peers

In 2005, Dr. Jennifer Brull figured that she needed to get on board with health IT, even though it might be expensive and difficult for a family physician in a rural Kansas solo practice. A younger physician with whom she was collaborating suggested that having an EHR was the wave of the future, and would likely be a necessity going forward. She also had a practice-sharing arrangement with another physician, who was older. He was not as sure, Dr. Brull said in an interview.

But they moved ahead and spent 3 years selecting, buying, and implementing an EHR system that they could all use, said Dr. Brull, who practices in Plainview. She took out a loan for \$50,000 to buy the equipment; her colleagues contributed to the software and other costs.

Because they practice in a rural area, there was no possibility of using a Web-based model; broadband access in her area is still not robust enough, said Dr. Brull. So she has a server onsite at her office, and recently purchased a second server for \$3,000. The net cost so far has been about \$30,000 per physician, Dr. Brull said.

The first 6 months were a challenge, she said. "Anytime you do something that's a complete paradigm shift, it's hard. It's hard mentally to think about all those changes, hard physically because you're investing more time and effort, and hard emotionally because your staff gets freaked out."

In addition to allowing the practice to meet meaningful use criteria, the system also has a patient portal. The physicians are preparing to be able to participate in the state's health information exchange.

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## Making Sense of Meaningful Use: How, Where, and When

The ONC provides the central leadership for the Medicare and Medicaid EHR incentive programs. The HITECH (Health Information Technology for Economic and Clinical Health) Act directly appropriated \$2 billion to the ONC to spend on incentives and administration of the program. The federal regulation governing the incentive program (some 800 pages) was issued in July 2010.

This year – 2011 – is the first year in which physicians can participate; they have until Oct. 1 to attest that they are meaningful users. To be eligible for incentive payments, physicians have to meet the meaningful use criteria for 90 consecutive days.

The criteria are being introduced in stages over the next 4-5 years. Stage 1 outlines what is expected in 2011 and 2012. Stage 2 was expected to be put into place in 2013, but in June, the Health IT Policy Committee of the Centers for Medicare and Medicaid Services voted to delay implementa-

tion until 2014, but only for physicians who were already participating.

Physicians who wait until 2012 or later would still be expected to meet stage 2 criteria in 2013.

Physicians who want to participate have to choose between the Medicare or Medicaid incentive program.

Those who take part in the Medicare program are eligible to receive incentive payments of \$44,000 over 5 years. However, the payments will be made only through 2016. Physicians who wait until 2012 to start would still earn the \$44,000 maximum; those who start later would receive prorated payments.

Physicians who practice in designated Health Professional Shortage Areas (HPSA) may be eligible for an additional 10% in each year's incentive payment.

Importantly, Medicare begins to penalize nonparticipating physicians starting in 2016.

The Medicaid incentives are more generous: A total of \$63,750 can be

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Dr. Brull said that she disagrees with physicians who say that adopting an EHR interrupts the workflow or comes between the physician and patient.

"I've found it easier to be more collaborative [with my patients]," she said. One example: She recently used an EHR-generated graph to show a patient that she had gained 40 pounds over 3 years. The graph made much more of an impression on the patient than Dr. Brull could have done by reading numbers off a paper chart, she said.

"This whole project has resulted in dramatic quality improvement for my practice," Dr. Brull added. Another example: She implemented a quality measure on breast cancer screening. Just by having a flag in the EHR, she went from screening 50% of patients to almost 100%. "Having the data at your fingertips makes you aware of where you do a good job and where you don't," Dr. Brull said.

In April, Dr. Brull collected the full Medicare incentive payment for 2011. Her colleagues weren't ready, but that didn't matter. Physicians can choose to attest to meaningful use on their own time frame, regardless of where their colleagues might be, she said.

Dr. Brull has become an evangelist for the power of the EHR and meaningful use. She was chosen to speak at a CMS press conference announcing the first round of Medicare incentive payments. And she is a member of the regional extension center in Kansas. The ONC also named her a "MUVer" – someone who serves as a local leader and adviser.

### The Reluctant Adopter

Dr. Michael Machen is one of the physicians who consulted with Dr. Brull. He practices with four other family physicians in nearby Quinter, Kan. (population, 980). The impetus for taking on an EHR came from his younger partners, Dr. Machen said in an interview. They were also motivated by the meaningful use program, and got started in July 2010.

One junior partner became the EHR champion, doing much of the legwork to find appropriate vendors and systems. The physicians also attended seminars and webinars offered by the Kansas Medical Society and the Kansas chapter of the AAFP. A team from the regional extension center visited their practice too, Dr. Machen said.

They borrowed \$75,000 to purchase

hardware and software. The biggest cost is the \$2,000-\$4,000 they spend monthly on IT support – a necessity when there is no one with such expertise in the practice or locally. The IT help comes from more than an hour away. Dr. Machen and his colleagues house the server themselves; broadband is no better in Quinter than it is in Plainview.

Dr. Machen said that the younger physicians have all done well with the system, but he is struggling.

"I'm not technically inclined, and I have very little computer knowledge," he said. It has also been difficult for his

nurse, who is spending more time on data entry and less on interacting with patients, Dr. Machen said, adding that they are both in their late 50s and are more frustrated with the system than are their younger colleagues.

His staff has been happy; there's no more searching for charts, and coding is easier, he said. And he does see the potential for improving quality, especially with the data-collection effort, warnings about drug interactions, and prompts for screening tests.

But for now, "it's horrible with the workflow and the patient flow." On days

of 15-20 patient visits, using the EHR is not as much of an issue. But on days of 30 patient visits, "it's not doable," he said.

So far, patients haven't been wild about the transition, either. They don't like the physician to be working on a computer during the visit, he said. And "I don't like it much, either," said Dr. Machen. "When I was in medical school, I was taught that the second you enter the exam room, the patient has your undivided attention." That's not really possible with an EHR, at least the way he sees it currently, although he also can see possible solutions, such as having a scribe. ■



Tablets/Oral Solution  
Rx Only

#### Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda.

#### INDICATIONS AND USAGE

Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

#### CONTRAINDICATIONS

Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

#### PRECAUTIONS

**Information for Patients and Caregivers:** Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

#### Neurological Conditions

Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

#### Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

#### Special Populations

##### Hepatic Impairment

Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

##### Renal Impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

#### Drug-Drug Interactions

**N-methyl-D-aspartate (NMDA) antagonists:** The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

**Effects of Namenda on substrates of microsomal enzymes:** *In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

**Effects of inhibitors and/or substrates of microsomal enzymes on Namenda:** Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

**Acetylcholinesterase (AChE) inhibitors:** Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

**Drugs eliminated via renal mechanisms:** Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotinic, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®.

**Drugs that make the urine alkaline:** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

#### Carcinogenesis, Mutagenesis and Impairment of Fertility

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m<sup>2</sup> basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro* S. typhimurium or E. coli reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m<sup>2</sup> basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

#### Pregnancy

**Pregnancy Category B:** Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m<sup>2</sup> basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Nursing Mothers

It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

#### Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

#### ADVERSE REACTIONS

The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

**Adverse Events Leading to Discontinuation:** In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

**Adverse Events Reported in Controlled Trials:** The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

**Vital Sign Changes:** Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

**Laboratory Changes:** Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

**ECG Changes:** Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

#### Other Adverse Events Observed During Clinical Trials

Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized

categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1. WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

**Body as a Whole:** *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

**Cardiovascular System:** *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

**Central and Peripheral Nervous System:** *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

**Gastrointestinal System:** *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

**Hemic and Lymphatic Disorders:** *Frequent:* anemia. *Infrequent:* leukopenia.

**Metabolic and Nutritional Disorders:** *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

**Psychiatric Disorders:** *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paranoia, delirium, depersonalization, neurosis, suicide attempt.

**Respiratory System:** *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

**Skin and Appendages:** *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

**Special Senses:** *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

**Urinary System:** *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

#### Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US

Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, aortic/arterial block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

#### ANIMAL TOXICOLOGY

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

#### DRUG ABUSE AND DEPENDENCE

**Controlled Substance Class:** Memantine HCl is not a controlled substance.

**Physical and Psychological Dependence:** Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

#### OVERDOSAGE

Signs and symptoms associated with memantine overdose in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.



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