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HEALTH SCOPE

A Quarterly Publication of
Employers Health Coalition of Ohio, Inc.

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- 8 Transforming Ohio's Healthcare System



February 18**8:00am-Noon****PBM 101 (Central OH)**

OCLC Conference Center - Dublin, OH
(Breakfast/Registration 8:00- 8:30am)

March 3**Mercer's National Survey of Employer Sponsored Health Plans**

Northeast Ohio

8:00-9:30am

Barette Business Center at Walsh University
(Breakfast/Registration 8:00-8:30am)

Central Ohio

3:00 -4:30pm

Longaberger Alumni House, Columbus OH
(Light refreshments will be provided)

March 17**7:30am-4:30pm****PBM Academy (Central OH)**

The Conference Center at NorthPointe
(Breakfast/Registration 7:30- 8:00am)

April 3**8:00-10:30am****The Benefits of****Advanced Practice Nurses (Northeast OH)**

Glenmoor Country Club
(Breakfast/Registration 8:00-8:30am)

Mark Your Calendar and Keep an Eye on
 Our Website for Additional Future Events!

www.ehpc.com

Welcome to the Winter 2009 edition of HealthScope.



Dear Members and Friends,

As we ended the year of celebrating the 25th Anniversary of the Coalition, we entered the future with excitement and rejuvenation. You will, or perhaps have already, noticed some adjustments to the logo and branding of the Coalition. This new mark brings a fresh perspective to the look and feel of our materials and to the image of the organization. Many of our efforts, as well as those of our members, are focused around health and productivity. The apple included in the new logo very much encompasses this as well as our commitment to education and support of our many valued partnership with all of you.

In this issue of HealthScope, Bruce Sherman links workforce productivity to employee assistance programs (EAPs); Charity Rausch provides some insight around creating an effective health promotion program; Dave Uldricks provides an overview of a three-day summit that our organization helped sponsor with the Health Policy Institute of Ohio entitled, Transforming Ohio's Healthcare System; and Maracas Miles provides a spotlight on two new directors who join the Board, effective January 1, 2009. Thus, we extend a warm welcome to Chris McSwain of Whirlpool Corporation and Greg Troy of Modine Manufacturing, and thank Peg Breetz of FirstEnergy for her continued participation on the Board. We recognized the retirement of Tim Schiltz, PhD, of Whirlpool Corporation, at our Annual Meeting in early December. Tim served on our Board for a total of 21 years representing The Hoover Company, Maytag Corporation and Whirlpool.

Some member news worthy of sharing highlights both the City of Dublin and Franklin County. The City of Dublin was recently selected as the "Gold" Corporate Winner at the second annual Akron General Wellness Champion Awards. Akron General Wellness Champion Awards is a prestigious program honoring community leaders, individuals and corporations/organizations, who have made impressive strides toward improving personal health or the health of employees. Franklin County was honored as a recipient of the UnitedHealth Wellness® "Well Deserved" award, an employer wellness recognition program of UnitedHealthcare. Franklin County was tops among ten national recipients demonstrating the highest level of commitment to workplace wellness while leveraging the most UnitedHealth Wellness programs, tools and resources. Congratulations to both of these Coalition members.

I want to thank Forrest Pharmaceuticals, this month's HealthScope sponsor. Also, you will notice a new look and design of HealthScope beginning with this issue. The change is a result of our bringing the production in-house, which coincides with the launch of our new trademark. Heres to a great beginning of the New Year!

Sincerely,

Christopher V. Goff, Esq.

CEO & General Counsel

Employers Health Hosts Annual Meeting

The 2008 Annual Meeting of the Board of Directors took place on Tuesday, December 2 at Glenmoor Country Club.

In addition to the annual business meeting, election of new directors and Coalition updates, a keynote presentation was provided by Greg Paradiso, Director, Compensation & Benefits at Coalition member company, Glatfelter.

The focus of the Annual Employer Symposium in May 2009 will center around on-site medical clinics, with a variety of different examples to be presented. As a precursor to that meeting, Paradiso was invited to speak about Glatfelter's experience with an on-site primary care center at its Chillicothe, Ohio manufacturing facility. Paradiso talked about his team's experience in measuring and improving the ROI of the primary care center.

In addition to a traditional health plan offering, Glatfelter makes available to its employees a Glatfelter Family Medical Center (GFMC) Plan. The GFMC plan offers a greatly reduced annual premium over the traditional plan, as well as at least a 50% reduced co-payment rate across the board. Since the inception of the GFMC plan, the company has seen an enrollment increase of 11% among salaried employees over a two-year period, and a 34% increase in enrollments among union workers over just a one-year period.

When measuring the ROI for community versus on-site medical costs in 2007, the company saw an avoidance of 3.7 million dollars. The avoided pharmacy costs for that same period are calculated at



Chris Goff thanks Tim Schiltz for his service to the Employers Health Board of Directors.

860 thousand dollars. The combined avoided costs total nearly 4.6 million dollars from operating the Family Medical Center. Glatfelter hopes to see about a 28% increase in avoided costs for 2008.

During the meeting, two new directors were elected. Chris McSwain, Director, Human Resources Global Benefits for Whirlpool Corporation and Greg Troy, VP/Chief Human Resource Officers for Modine Manufacturing will each serve a two-year term. Current board member, Peg Breetz, Manager, Benefits & Compliance for FirstEnergy was re-elected for a third consecutive two-year term.

Tim Schiltz, who served Employers Health and its members for 21 years, and recently retired from the Board, was recognized during the meeting. The longest serving member ever, Tim made a commitment over the years to furthering the agenda of employers, and to the growth of the Coalition.

Flu Shots Offered to Member Companies

As a way to provide additional value to its members, Employers Health decided last year to make available flu shots. The goal was to provide members with a more affordable option than might otherwise be found in the marketplace. The vaccine was procured through Glaxo Smith Kline (GSK), thanks to a great partnership with Scott Smith and Steve Stitt, account team at GSK. Another way to make this an effective option for members was the availability of Employers Health director, analytics and clinical initiatives, Charity Rausch R.Ph., to administer the vaccine. Seven member companies took advantage of the flu shots, with a total of 1,055 vaccinations administered. Due to the success of the 2008 offering, Employers Health will make this service available again in 2009.

Participating members included:

- Diebold
- FirstMerit
- Mantaline
- Marlite
- OCLC
- OMNOVA Solutions
- PRC



Charity Rausch, R.Ph. administers a flu shot to an OMNOVA Solutions employee.

Employee Assistance Programs

A Value-Generating Investment in Workforce Health and Productivity



BY BRUCE SHERMAN, MD, FCCP

Recently, consumer directed health plans have become increasingly popular as a means to promote wiser use of healthcare resources. The rationale is that individuals with a greater financial stake in healthcare decision making will adopt a more consumer-oriented approach to healthcare. Makes sense? Perhaps not.

Now more than ever, employers are looking at workforce health strategies as a means to enhance work productivity and business profitability. However, it can be difficult to accurately identify specific health concerns within a benefits-eligible population that would benefit from focused programming such as disease management. Furthermore, while there may be some benefit from this type of program, the eligible population is typically small, thereby minimizing the absolute financial return on investment. And to make matters worse, the majority of health management programs promise largely longer-term cost savings due to avoidance of disease-specific complications.

So what if there were another type of program that offered potential benefit to the entire workforce and family members, was provided at a fixed cost, and promised near-term benefit? Employee assistance programs (EAPs) may well be just that. EAPs have been around for a number of years, with roots in alcohol and drug abuse rehabilitation. During the past twenty years, they have evolved into a more significant benefit that can improve health and productivity, reduce costs and risks, and is aligned with both employee and employer interests.

Today's EAPs offer a menu of employer support services, including:

- Behavioral issues affecting home life, work relationships, stress, depression
- Work-life services – financial, legal, child/eldercare
- Substance abuse rehabilitation support
- Employer consultative support for policy issues, disciplinary and legal/regulatory concerns
- Employee training programs

Yet many employers have been slow to fully appreciate the potential impact – and value – that an EAP can provide. Perhaps one of the most obvious reasons is that it is difficult to measure the cost savings that an EAP can yield. Unlike healthcare cost savings, there are no specific financial measures directly

associated with EAP use, and with the broad array of provided services, quantifying a return on investment is elusive, at best.

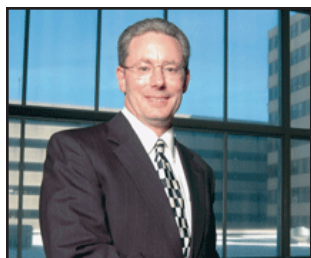
Nonetheless, there is ample evidence that people with stress and depression have higher non-behavioral healthcare costs. Depression can play a major role in chronic conditions such as diabetes and heart disease, and undoubtedly contributes to prolonged absence due to medical illness and work-related injury. Investing in an EAP offering can help mitigate these costs, particularly when the program is effectively integrated with other health benefits.

In the current economic climate, job insecurity can further contribute to or exacerbate behavioral issues. For employers that currently have an EAP, consider expanding the visibility of this benefit for your employees and their family members to address current fears and concerns. For employers who are considering the addition of an EAP offering to their health benefits, it's important to recognize that the associated fees of less than \$2 per employee per month compare favorably with such services as chiropractics (about \$4 PEPM).

Finally, with the current fixed fee pricing model for most EAPs, increased utilization and the associated health and productivity benefits won't cost a penny more.

Coalition Welcomes Two New Board Members

Employers Health is pleased to welcome two new members to its Board of Directors. Chris McSwain, Director, Human Resources Global Benefits for Whirlpool Corporation and Greg Troy, VP/Chief Human Resource Officer for Modine Manufacturing were elected at the Annual Meeting.



Chris McSwain joined Whirlpool Corporation in December of 2007, as Director, Global Benefits. In January 2008, Business Insurance Magazine named him one of the “2008 People to Watch.” Before joining Whirlpool, Chris served as Director, Compensation and

Benefits for SCANA Corporation. He accomplished a great deal at SCANA, and Business Insurance Magazine named Chris the 2005 Benefits Manager of the Year. For the past 20 years, Chris has served in various human resource capacities with companies such as Novartis, Syngenta, Oakwood Homes, General Dynamics and Reichhold.

When asked about the goals for his division in 2009, Chris says that he aims to use innovation to improve Whirlpool’s pharmacy spend by 20-30%. Other plans include more strategic communication to employees and more effective supplier management. “By better communicating with employees, we hope that we can help them better understand that they own their health, wealth and career,” said Chris.

Chris brings a strong willingness to partner to the Coalition. He plans to utilize the power of the Coalition to leverage mutual strengths. “I have the highest regard for the functional and technical capabilities that the Coalition brings for my needs,” said Chris, “the Coalition is truly an extension of my benefits team.”

As a seasoned benefits expert, he says that when working in this field, “do not take your eyes off the prize,” which he sees as the improved health and productivity of the workforce. “Keep focused on the real people behind the numbers, they rely on us to help them,” said Chris. He also believes that it’s important to not be afraid to take a risk. “Be bold,” he says, when working with internal constituents and external vendors. Finally, Chris adds that he truly believes that “our people, the human capital, are the final differentiation in the marketplace.”



Greg Troy is no stranger to Employers Health, having served on the Board of Directors previously while working for OMNOVA Solutions in Fairlawn, OH. Greg joined Modine Manufacturing, in Racine Wisconsin, in February 2006, and is responsible for leading the company’s global human resources function.

In addition to OMNOVA, Greg has also served at Gencorp, Inc., Bosch Braking Systems, Mobil Corporation, Printpack, Inc., and Cabledata, Inc. He also served as an officer in the U.S. Army with the rank of Captain, following a four-year Army ROTC scholarship.

Modine’s focus for 2009 will be to keep priority on organizational alignment and cost initiatives. “We make a variety of heat thermal transfer products for the automotive, agricultural and off-highway markets,” said Greg. “Our industrial sector business has strong pressures on it globally, and we will be executing to an operating plan that is cost effective and streamlined,” he says. This includes Modine’s benefits strategy and its dashboard metrics with key providers: UnitedHealthcare, CVS Caremark and NEAS (employee assistance).

“I am honored to serve on the Board of Directors and hope to bring an inclusion of ideas and challenges that our business faces to the Board for consideration,” said Greg. He feels that organizations, whether public, private or non-profit, confront the tugs of providing affordable health and wellness programs while balancing the increasing costs of these services.

Modine has benefited tremendously in the two and a half years it has been a member of the coalition, primarily in leveraging its prescription purchases and in educating its senior management and human resources group. “We are excited to participate in the data warehouse project to further expand our knowledge of disease management and wellness initiatives,” Greg included.

Greg believes that in today’s environment, you must ingrain your efforts in the strategy of your business and provide solutions to senior management on how the organization’s benefit and wellness strategies can make a financial impact. “Our time is now, especially as the economy is struggling, to make a difference on influencing the future for our employees,” said Greg.

Creating an Effective Health Promotion Program



BY CHARITY RAUSCH, RPH

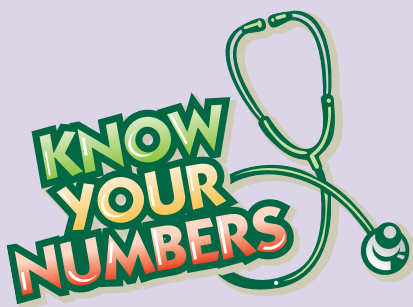
Chronic disease, which can largely be preventable, accounts for about 80% of the burden of disease / illness and 90% of all medical costs. Preventable illnesses and chronic disease account for eight of the nine leading causes of death.

The United States spends more on health care than any other industrialized nation in the world. Medical care costs in the United States exceed 14% of the gross domestic product.

Wellness programs are based on the belief that unhealthy lifestyles can be changed with the right support structure. Whether the issues involve smoking cessation, stress management, obesity or depression, targeted programs based on the latest advances in behavioral health research and technology are providing employers

with increasingly effective and affordable methods for improving workforce health and productivity.

Planning a worksite health promotion program can be a rewarding experience for company leaders and other employees. Whether an employer decides to develop a comprehensive worksite health promotion program all at once, or begin with just a few ongoing health promotion activities, it will be helpful to use a planning process.



If you and your employees are trying to eat healthier foods and get in a little more exercise, good for you! Now there's one more thing to do to assure a healthier life: know your numbers - not just your height and weight, but also your blood pressure, cholesterol and blood sugar levels.

Kits for Know Your Numbers are now available to EHPCO member companies for use with their wellness efforts. The kit includes a folder with educational materials around common conditions such as cardiovascular disease, diabetes and obesity, as well as information on prevention and maintenance of the specific disease states. A handy pocket card for tracking the important numbers that you need to know is also included in the kit.

For a sample of the kit, email Coleen Gehring at cgehring@ehpco.com or visit the Know Your Numbers portion of our website at: www.ehpco.com/knowyournumbers.

Here is a simple 10-step process that can be used by employers of all sizes to increase the success of any health promotion program.

1. Capture senior level support for the wellness program

Build the business case for the wellness of the employees' health and job satisfaction.

2. Build a wellness program team

Select from employees interested in health promotion or seek to hire outside professional assistance.

Look for people who can continually motivate and educate employees.

3. Assess the interests and needs of corporate leaders and other employees

Evaluate all data sources to identify greatest opportunities for health improvement.

Present surveys to management and employees.

4. Develop a mission statement, goals and objectives and design the program

Establish a clear vision of the program direction and expectations.

Identify two to five clearly stated goals for the program.

Design a program that will target the needs and appropriate health risks of the employees.

5. Develop a timeline and budget

Develop a realistic timeline to implement and evaluate the program.

Develop a comprehensive budget for the program to include salaries for staff, vendors, program materials, and administrative costs.

6. Select incentives

Identify what incentives are most valued by employees.

Reward use of program features and preventive services.

7. Acquire resources

Find a health program vendor that will fit the needs of the employees.

Reach out to pharmaceutical companies that market disease management programs.

Recruit free speakers from the community for health awareness activities.

8. Market the program

Involve employees in the name of the program so there is some sense of ownership of the program.

Communicate often by email, bulletin board and newsletter announcements which are free or inexpensive.

9. Implement the program

Implementing the program involves putting the plan into action.

Work with health promotion vendor, health plan, and recruit speakers, or schedule health promotional activities to kick-off an implementation to get excitement in the workplace for the program.

10. Evaluate and modify program (continuous quality assurance)

Review information that has been gathered to evaluate how the program is working and if it is achieving expected goals.

Outcomes can be used to modify the program and enhance participation and satisfaction.



Recent Summit Addresses the Issues Transforming Ohio's Health Care System



BY DAVID ULDRICKS, JD, LLM

The top strategies that will transform Ohio's health care system into a high quality, cost-effective, high performing system were identified by leaders across the health care industry during the Ohio Health Quality Improvement Summit held in Columbus, Ohio on November 17 – 19, 2008.

During the three-day summit, participants listened to nationally renowned speakers on health care reform and separated into four multi-stakeholder work groups to identify and refine the strategies that will yield the greatest positive impact by 2013. Each work group focused on developing strategies and supporting tactics in one of the following focus areas:

- 1) Improving Chronic Care Management,
- 2) Promoting Health through Personal Responsibility and Disease and Injury Prevention,
- (3) Improving Patient Safety and Reducing Errors, and
- (4) Improving Efficiency and Decreasing Cost in the Health care System.

The specific tactics developed by each work group in support of its strategies considered each of the following:

- (1) Health information technology,
- (2) Payment reform,
- (3) Health disparities, and
- (4) Workforce development.

After each work group developed its top strategies and supporting tactics, all of the participants in the Ohio Health Quality Improvement Summit re-convened as a whole to vote on the strategies developed by each work group. Each participant received twenty votes that could be allocated to any of the strategies, provided that at least one vote was cast for at least one strategy in each of the four focus areas.

The Ohio Health Quality Improvement Summit was the result of a series of events stemming back to early 2008.

In early 2008 the State of Ohio applied to participate in the Commonwealth Fund / Academy Health State Quality Improvement Institute based on Governor Strickland's vision for a healthy Ohio, the state legislature's interest in addressing concerns about cost and quality, multi-stakeholder interest in addressing systemic issues beyond health

insurance coverage, local quality improvement initiatives, and national research illustrating opportunities for improvement.

In April 2008, Ohio was chosen as one of nine states to participate in the State Quality Improvement Institute initiative. As part of the proposal process, each state was asked to identify two indicators on which to focus from the Commonwealth Fund's State Scorecard on Health System Performance. After meeting with several experts, the Ohio State Quality Improvement Institute initiative team concluded that choosing two indicators and then trying to build buy-in from stakeholders would not be effective, and the two chosen indicators may not have the greatest potential for return on investment and together do not create a balanced portfolio.

As a result, the Ohio Health Quality Improvement Summit was created to pull together a diverse group of stakeholders to coalesce around a portfolio of strategies that offer opportunities for short and long term return on investment (in both human and monetary terms), to which a wide array of stakeholders can commit in terms of action, and may be informed by a variety of local initiatives that are ongoing throughout the state.

The results of the voting and top five strategies developed and selected by the Ohio Health Quality Improvement Summit.

Strategy	Vote Count	Percent of Vote
Advance a sustainable, community-specific Chronic Care Model with a prepared, proactive practice team and an informed and activated patient focused on improved outcomes.	487	18.1%
Promote a culture of physical and emotional health and wellness through lifestyle options that comprehensively address decreasing the prevalence of the most pressing population health issues: Depression, Obesity and Tobacco use.	348	12.9%
Transform healthcare delivery through patient centered primary and preventative care.	348	12.9%
Increase the percentage of Ohioans receiving the recommended primary and secondary preventative health services appropriate to the individual's age, gender and condition.	230	8.5%
Reduce or eliminate preventable error rates and improve communication during hand-offs and transitions.	192	7.1%

Employers Health Staff Participate in Local and National Presentations & Programs

Bruce Sherman

- Employers Need Strategies, Vendors Sell Programs: How to be an Effective Partner. ProfSoft University, Burlington, VT, 2008.
- Smoking Cessation: The Purchaser Perspective – A Valuable Health Benefit. The Executive Forum on Value-Based Benefits Design for Employers. Philadelphia, PA, 2008.
- Critical Thinking about the Value Based Approach to Benefits and Wellness. Fourth Annual High Performance Benefits & Wellness Forum, Dallas-Ft. Worth Business Group on Health, Dallas, TX, 2008.
- Smoking Cessation: The Purchaser Perspective – A Valuable Health Benefit. Columbus, OH/Lexington, KY 2008.
- On-Site Clinics: Increased Quality and Employee Engagement while Lowering the Cost of Care. National Business Group on Health, San Diego, 2008.

Chris Goff

- PBM Evaluation Strategies, co-presented with Randy Vogenberg Ph.D., R.Ph. at the National Business Coalition on Health Annual Conference, Washington DC.
- Value-Based Benefit Design - Presented to the Arizona Geriatrics Society, Phoenix, AZ.

Treat today with NAMENDA

Proven efficacy and tolerability




- Improves function, delays onset of behavioral symptoms, and provides benefits in cognition^{1,3}
- Proven safety and tolerability with low risk of gastrointestinal side effects may improve therapy persistence^{4,5}
- Reduces caregiving time, cost, and caregiver distress^{3,6,7}
- Effective first-line and in combination with an acetylcholinesterase inhibitor^{1,2}

Broad patient access—covered on 98% of Medicare Part D formularies⁴

NAMENDA® (memantine HCl) is indicated for the treatment of moderate to severe Alzheimer's disease.

NAMENDA is contraindicated in patients with known hypersensitivity to memantine HCl or any excipients used in the formulation. The most common adverse events reported with NAMENDA vs placebo ($\geq 5\%$ and higher than placebo) were dizziness, confusion, headache, and constipation. In patients with severe renal impairment, the dosage should be reduced.

Namenda 
memantine HCl
Extending memory and function

References: **1.** Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.* 2003;348:1333-1341. **2.** Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA.* 2004;291:317-324. **3.** Cummings JL, Schneider E, Tariot PN, Graham SM, for the Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology.* 2006;67:57-63. **4.** Data on file. Forest Laboratories, Inc. **5.** NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo. **6.** Wimo A, Winblad B, Stöffler A, Wirth Y, Möbius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics.* 2003;21:327-340. **7.** Winblad B, Poritis N. Memantine in severe dementia: results of the ⁹M-BEST Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry.* 1999;14:135-146.

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For more details, please visit www.namenda.com.
Please see brief summary of Prescribing Information on the adjacent page.

62-1014307R R1

09/08

Namenda

memantine HCl



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 nicotine, 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/m² 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/m² 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/m² 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/m² 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/m² 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, infected 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 decreased, 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, asthma, 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, incontinence, 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/m² 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 overdosage 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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Rev. 04/07

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HealthScope is published quarterly. EHCO was founded in 1983 as a 501(c)(3) not-for-profit corporation. Its mission is to create an environment for long-term continuous improvement in the cost-effective delivery of high quality health care services for its members and the communities it serves.

Marcas Miles, Editor
Design by Grabowski & Co.

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