

CMS 'E-Prescribing' Rule Presents Big Challenges

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Without the proper technology, physician practices may find it difficult to participate in Medicare's new "e-prescribing" standards under the Part D drug benefit, physician groups claim.

"Most primary care physicians will be unable to afford to implement this technology on their own, particularly with

the projected cuts in Medicare physician payments of 4.4% in 2006 and a cumulative 26% reduction from 2006 to 2011," Neil Kirschner, Ph.D., senior associate for regulatory and insurer affairs with the American College of Physicians, said in an interview.

The Centers for Medicare and Medicaid Services in a final rule established the set of standards for electronic prescribing, or e-prescribing, of drugs covered by Medicare's prescription drug benefit that started Jan.

1, according to the Federal Register.

CMS also plans to pilot test initial e-prescribing standards, which may be included in a final rule to be issued by April 2008.

"These standards will allow Medicare, physicians, hospitals, group practices, other health providers, and prescription drug plan sponsors and Medicare Advantage organizations to take advantage of e-prescribing technology to improve medication prescribing for Medicare beneficiaries that participate in the new prescription

drug program," said Mike Leavitt, secretary of the Department of Health and Human Services.

For the most part, medical organizations expressed support for the agency's e-prescribing initiative. "Having standards is good. It will provide a common language for anyone using this method," Dr. Mary Frank, board chair of the American Academy of Family Physicians, said in an interview. E-prescribing would also reduce errors, increase patient safety, and when it is fully interoperable, increase quality in health care as well, she said.

Unfortunately, few practices are using this technology, Dr. Kirschner said. "Surveys vary, but the percentage of practices using it ranges somewhere from 5% to 18%." The number is even lower for the typical small practice, he added.

Only 25%-30% of the AAFP's members have electronic health records, Dr. Frank said. "They are, at present, the only ones who might be able to immediately adopt this approach. I say 'might' because not all EHR systems have the e-prescribing component." Until there is some financial support to help doctors implement this technology, it will not be used widely, she said.

Even if a physician does have the money to adopt e-prescribing, "he or she is at risk of purchasing a system that might not integrate" with a future electronic health record system, she said.

Dr. Kirschner noted that the recent release of safe harbor antikickback and Stark exception rules allowing hospitals, group practices, and Medicare Part D drug plan sponsors to provide necessary e-prescribing technology to physicians may help facilitate its use.

Although e-prescribing may eliminate issues such as bad handwriting and sound-alike medications, it doesn't necessarily address issues such as drug-drug interactions, alerts about possible problems related to existing illnesses, or abnormal lab results, said Dr. Frank. "We really have to push for a more integrated approach if we really want to improve care," she said.

E-prescribing is optional for physicians and pharmacies under the new standards, but as of Jan. 1, 2006, Medicare required drug plans participating in the new prescription benefit to support electronic prescribing.

Jeff Trewhitt, a spokesperson for the Pharmaceutical Research and Manufacturers of America, said PhRMA supported the development of a standardized e-prescribing system. In addition to reducing errors and the administrative costs associated with health care, the system would also promote more effective care of drug therapies for chronic conditions.

He agreed, however, that such a system must be designed and implemented correctly. "Keep in mind that the systems needed to convert to an e-Rx system don't even exist yet."

CMS's new standards for e-prescribing include the following technology: NCPDP SCRIPT, Version 5.0; ASC X12N 270/271, Version 4010 and addenda; and NCPDP Telecommunication Standard, Version 5.1, and supporting NCPDP Batch Standard, Version 1.1. ■

BIDIL® (isosorbide dinitrate/hydralazine HCl)

INDICATIONS AND USAGE

BIDil is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. There is little experience in patients with NYHA class IV heart failure. Most patients in the clinical trial supporting effectiveness (A-HeFT) received a loop diuretic, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker, and many also received a cardiac glycoside or an aldosterone antagonist.

CONTRAINDICATIONS

BIDil is contraindicated in patients who are allergic to organic nitrates.

WARNINGS

Augmentation of the vasodilatory effects of isosorbide dinitrate by phosphodiesterase inhibitors such as sildenafil, vardenafil, or tadalafil could result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Reasonable supportive care should consist of those measures used to treat a nitrate overdose with elevation of the extremities and central volume expansion.

PRECAUTIONS

General

The precautions that need to be taken when using BIDil are those appropriate to each of its components.

Treatment with hydralazine hydrochloride may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis. If systemic lupus erythematosus-like symptoms occur in patients treated with BIDil, discontinuation of BIDil should be considered only after a thorough benefit-to-risk assessment. Symptoms and signs of systemic lupus erythematosus usually regress when hydralazine hydrochloride is discontinued but residual have been detected many years later. Long-term treatment with steroids may be necessary. (See PRECAUTIONS, Laboratory Tests.)

Symptomatic hypotension, particularly with upright posture, may occur with even small doses of BIDil. Therefore, BIDil should be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hydralazine hydrochloride can cause tachycardia potentially leading to myocardial ischemia and anginal attacks.

Careful clinical and hemodynamic monitoring is recommended when BIDil is administered to patients with acute myocardial infarction to avoid the hazards of hypotension and tachycardia.

Hydralazine hydrochloride has been associated with peripheral neuritis, evidenced by paresthesia, numbness, and tingling, which may be related to an antipyridoxine effect. Pyridoxine should be added to BIDil therapy if such symptoms develop.

Isosorbide dinitrate therapy may aggravate angina associated with hypertrophic cardiomyopathy.

Information for Patients

Patients should be informed of possible side effects and advised to take the medication regularly and continuously as directed. Patients should be told that headaches often accompany treatment with BIDil, especially during initiation of treatment. Headaches tend to subside even with continued dosing. Patients should be instructed to consult a physician to adjust the dose of BIDil if headache continues with repeated dosing. Treatment of emerging headache was managed with acetaminophen in some clinical trial patients.

Treatment with BIDil may be associated with lightheadedness on standing, especially after rising from a recumbent or seated position.

Patients should be cautioned that inadequate fluid intake or excessive fluid loss from perspiration, diarrhea or vomiting may lead to an excessive fall in blood pressure and cause lightheadedness or even syncope. If syncope does occur, BIDil should be discontinued, and the prescribing physician should be notified as soon as possible.

Patients should be cautioned about the increased risk of hypotension especially if they are taking antihypertensive drugs concomitantly.

Patients should be cautioned against concomitant use of BIDil with phosphodiesterase-5 inhibitor drugs used for the treatment of erectile dysfunction or pulmonary hypertension such as sildenafil citrate (Viagra®; Revatio®), vardenafil (Levitra®) or tadalafil (Cialis®). Use of BIDil may produce an extreme drop in blood pressure that may result in fainting or may provoke chest pain or a heart attack.

Laboratory Tests

If symptoms suggestive of systemic lupus erythematosus occur, such as arthralgia, fever, chest pain, prolonged malaise, or other unexplained signs or symptoms, complete blood counts and antinuclear antibody titer determinations should be performed. A positive antinuclear antibody titer requires that the physician carefully weigh the benefits and risks of continued therapy with BIDil.

Drug/Drug Interactions

Due to the hydralazine component of BIDil, monoamine-oxidase inhibitors should be used with caution in patients receiving BIDil. Patients treated with BIDil who receive any potent parenteral antihypertensive agent should be continuously observed for several hours for excessive fall in blood pressure.

The effects of BIDil on vasodilators including alcohol may be additive.

Sildenafil: See WARNINGS.

Vardenafil: See WARNINGS.

Tadalafil: See WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydralazine Hydrochloride

An increased incidence of lung tumors (adenomas and adenocarcinomas) was observed in a lifetime study in Swiss albino mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 250 mg/kg per day (6 times the MRHD provided by BIDil on a body surface area basis). In a 2-year carcinogenicity study of rats given hydralazine hydrochloride by gavage at dose levels of 15, 30, and 60 mg/kg/day (up to 3 times the MRHD of BIDil on a body surface area basis), microscopic examination of the liver revealed a small, but statistically significant increase in benign neoplastic nodules in males (high-dosage) and females (both high and intermediate dosage groups). Benign interstitial cell tumors of the testes were also significantly increased in the high-dose group.

Hydralazine hydrochloride is mutagenic in bacterial systems, and is positive in rat and rabbit hepatocyte DNA repair studies *in vitro*. Additional *in vivo* and *in vitro* studies using lymphoma cells, germinal cells, fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic or clastogenic potential for hydralazine hydrochloride.

Isosorbide Dinitrate

No long-term animal studies have been performed to evaluate the mutagenic or carcinogenic potential of isosorbide dinitrate. A modified two-litter reproduction study among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day (up to 9 times the Maximum Recommended Human Dose of BIDil on a body surface area basis) revealed no evidence of altered fertility or gestation.

Pregnancy Category C

Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (excess mummified pups) in rabbits at 70 mg/kg (12 times the MRHD of BIDil on a body surface area basis). Hydralazine hydrochloride is teratogenic in mice at 66 mg/kg and possibly in rabbits at 33 mg/kg (2 and 3 times the MRHD of BIDil on a body surface area basis). There are no animal studies assessing the teratogenicity of BIDil.

A meta-analysis of randomized controlled trials comparing hydralazine hydrochloride with other antihypertensive agents for severe hypertension in pregnancy found that hydralazine hydrochloride was associated with significantly more maternal hypotension, placental abruption, caesarean sections and oliguria, with more adverse effects on fetal heart rate and with lower Aggar scores.

A combination of propranolol and hydralazine hydrochloride was administered to 13 patients with long-standing hypertension during 15 pregnancies. These pregnancies resulted in 14 live births and one unexplained stillbirth. The only neonatal complications were two cases of mild hypoglycemia. Hydralazine hydrochloride and its metabolites have been detected using a non-selective assay in maternal and umbilical plasma in patients treated with the drug during pregnancy.

Isosorbide dinitrate has been used for effective acute and sub-chronic control of hypertension in pregnant women, but there are no studies using it in a chronic regimen and assessing its effects on pregnant women and/or the fetus.

There are no studies using BIDil in pregnant women. Therefore, BIDil should be used with caution during pregnancy and only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

The possible excretion of hydralazine in breast milk has not been determined. It is also not known whether isosorbide dinitrate is excreted in human milk. No studies have been performed with BIDil. Caution should be exercised when BIDil is administered to a nursing woman.

Pediatric use

The safety and effectiveness of BIDil in children have not been established.

Geriatric use

Clinical studies of BIDil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic and renal function, and of concomitant disease or other drug therapies.

Isosorbide dinitrate, its active metabolites, and hydralazine may be eliminated more slowly in elderly patients.

ADVERSE REACTIONS

BIDil

BIDil has been evaluated for safety in 517 heart failure patients in A-HeFT. A total of 317 of these patients received BIDil for at least 6 months, and 220 received BIDil for at least 12 months. In A-HeFT, 21% of the patients discontinued BIDil for

adverse experiences compared to 12% who discontinued placebo. Overall, adverse events were more common in BIDil-treated than in placebo-treated patients. Table 1 lists adverse events reported with an incidence of $\geq 2\%$ in patients treated with BIDil in A-HeFT, and, after rounding to the nearest 1%, occurring more frequently than in the placebo group, regardless of causality. Headache and dizziness were the two most frequent adverse events and were more than twice as frequent in the BIDil group. The most common reasons for discontinuing BIDil in the A-HeFT trial were headache (7%) and dizziness (4%).

Table 1. Adverse Events Occurring in the A-HeFT Study in $\geq 2\%$ of Patients Treated with BIDil.

	BIDil (N=517) (% of patients)	Placebo (N=527) (% of patients)
Headache	50	21
Dizziness	32	14
Chest pain	16	15
Asthenia	14	11
Nausea	10	6
Bronchitis	8	7
Hypotension	8	4
Sinusitis	4	2
Ventricular tachycardia	4	2
Palpitations	4	3
Hyperglycemia	4	3
Rhinitis	4	3
Paresthesia	4	2
Vomiting	4	2
Amblyopia	3	1
Hyperlipidemia	3	2
Tachycardia	2	1

The following adverse events were reported in A-HeFT in at least 1% but less than 2% of patients treated with BIDil, and also occurred in at least 0.5% more patients than in placebo-treated patients; all such events are included unless they are too non-specific to be meaningful or appear to reflect underlying disease.

Body as a Whole: Allergic reaction, malaise.

Central nervous system: Somnolence.

Gastrointestinal: Cholecystitis.

Metabolic: Hypercholesterolemia.

Musculoskeletal: Arthralgia, myalgia, tendon disorder.

Skin: Alopecia, angioedema, sweating.

In the V-HeFT I and II studies, a total of 587 patients with heart failure were treated with the combination of isosorbide dinitrate and hydralazine hydrochloride. The type, pattern, frequency and severity of adverse experiences reported in these studies were similar to those reported in A-HeFT, and no unusual adverse experiences were reported.

Prior experience with BIDil components

The following additional adverse events have been reported with hydralazine hydrochloride or isosorbide dinitrate but not necessarily with BIDil:

Digestive: paralytic ileus.

Cardiovascular: paradoxical pressor response, crescendo angina.

Neurologic: peripheral neuritis, numbness, tingling, muscle cramps, psychotic reactions, disorientation.

Genitourinary: difficulty in urination.

Hematologic: blood dyscrasias, agranulocytosis, purpura, splenomegaly.

Hypersensitive Reactions: eosinophilia, hepatitis.

Other: nasal congestion, flushing, lacrimation, conjunctivitis.

OVERDOSAGE

There are no documented cases of overdosage with BIDil. The signs and symptoms of overdosage with BIDil are expected to be those of excessive pharmacologic effect and those that may occur with overdosage of either isosorbide dinitrate or hydralazine hydrochloride administered alone.

Acute toxicity: No deaths due to acute poisoning have been reported.

Signs and Symptoms: The signs and symptoms of overdosage with BIDil are expected to be those of excessive pharmacologic effect, i.e., vasodilatation, reduced cardiac output and hypotension, and signs and symptoms include headache, confusion, tachycardia and generalized skin flushing. Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmia, and profound shock. Syncope, coma and death may ensue without appropriate treatment.

Treatment: There is no specific antidote.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders, vasopressors, and positive inotropic agents. The gastric contents should be evacuated, taking adequate precautions to prevent aspiration. These manipulations have to be carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide dinitrate overdose in these patients may be difficult, and invasive monitoring may be required. No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of the components of BIDil. Dialysis is not effective in removing circulating isosorbide dinitrate. The dialyzability of hydralazine has not been determined.

Methemoglobinemia

Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates.

Methemoglobin levels are measurable by most clinical laboratories. Methemoglobinemia could be serious in chronic heart failure patients because of already compromised vascular bed-tissue gas exchange dynamics. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

Treatment with BIDil should be initiated at a dose of one BIDil Tablet, 3 times a day. BIDil may be titrated to a maximum tolerated dose, not to exceed two BIDil Tablets, 3 times a day. There is no adequate experience in heart failure with doses of BIDil other than those recommended and no experience with the use of individual components.

Although titration of BIDil can be rapid (3-5 days), some patients may experience side effects and may take longer to reach their maximum tolerated dose. The dosage may be decreased to as little as one-half BIDil Tablet 3 times a day if intolerable side effects occur. Efforts should be made to titrate up as soon as side effects subside.

HOW SUPPLIED

BIDil Tablets contain 20 mg of isosorbide dinitrate plus 37.5 mg of hydralazine hydrochloride. They are biconvex, approximately 8 mm in diameter, scored, film-coated, orange tablets debossed "20" on one side over the score and "N" on the other side.

NDC 12948-001-12 bottle of 180.

Keep bottles tightly closed.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

[See USP Controlled Room Temperature.]

Protect from light. Dispense in a light-resistant, tight container.

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