

FDA Seeks Ways to Regulate Health Web Content

BY ALICIA AULT

At a meeting convened by the Food and Drug Administration, pharmaceutical and medical device manufacturers, advertisers, medical Web site owners, search engine companies, and consumer advocates all argued for greater regulation of health-specific content on the Internet, including social media sites.

The agency was seeking opinions on how it could guide health-related communications and promotions for YouTube, Twitter, blogging, and social networking sites. Notably, there were no speakers from any medical society or health care provider organization.

The FDA has not said when it might issue guidance, but it will continue to accept comments until Feb. 28, 2010, said Thomas W. Abrams, director of the FDA

Center for Drug Evaluation and Research's division of drug marketing, advertising, and communications.

All speakers agreed that consumers and health care providers increasingly rely on the Internet for information about drugs, devices, and specific conditions, and also to forge communities to share everything from caregiving recommendations to tips on how to perform a knee replacement.

All also agreed that there is a huge amount of inaccurate and misleading information and that it has a great potential for harm—to patients and their families, to health care providers, and to industries seeking credibility. Even as they seek to be the go-to place for accurate, scientific information, drug and device makers said they are wary—of social media in particular—because of the lack of FDA guidance.

Consumer groups raised the specter of pharmaceutical or device companies putting out purely promotional information that glosses over FDA rules requiring a fair balance of a product's risks and benefits.

Michele Sharp, senior director of United States Regulatory Affairs at Eli Lilly, said the company "had avoided significant interactions with providers and patients online" because of FDA's lack of clarity.

"We're looking to the FDA to provide leadership," Ms. Sharp said.

Jeffrey K. Francer, assistant general counsel for the Pharmaceutical Research and Manufacturers of America (PhRMA), said that "the FDA should facilitate manufacturers' communication of important medical information about their products in a responsible way, taking advantage of the same technologies that the FDA and the White House use, including blogs, video, search, and social networking sites such as Twitter."

PhRMA has proposed that posts on Twitter or blogs or other social media sites be accompanied by an official logo that would signify that the information was officially sanctioned by the FDA. Tweets, which are limited to 140 characters, could provide a hyperlink to the full risk and benefit information, Mr. Francer said.

He and other industry representatives said they wanted FDA to review information and promotional materials before they were posted on the Web. This would be a departure from current policy where only a small fraction of print or broadcast materials are reviewed in advance.

Some groups are trying to establish rules before FDA does. The Interactive Advertising Bureau said it was developing standards to provide "safe harbors" for the drug and device industry. IAB members provide 85% of online ads in the United States, said IAB representative David Wright. The Social Media Working Group has also been discussing what drug companies can do to self-police, said Mark Gaydos, chairman of the group and a regulatory affairs director at sanofi-aventis U.S. The group is made up of representatives from five pharmaceutical manufacturers who meet on a voluntary basis.

Google also proposed its own standards for "sponsored" searches. The search result would include a link to the official drug site and a link at the end, "more info," which would take users directly to the risk information, said Amy Cowan, head of industry for Google's health division. All results would also include a short warning statement. ■



WARNING: AVOID USE IN PREGNANCY
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, MICARDIS tablets should be discontinued as soon as possible. See Warnings and Precautions.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Hypertension: MICARDIS is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. **Cardiovascular Risk Reduction:** MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors. High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage. MICARDIS can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy). Studies of telmisartan in this setting do not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared. Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider re-trying the ACE inhibitor after the cough resolves. Use of telmisartan with an ACE inhibitor is not recommended.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Fetal/Neonatal Morbidity and Mortality: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue MICARDIS tablets as soon as possible [see Boxed Warning]. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second and third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, have the patient discontinue the use of MICARDIS tablets as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, MICARDIS should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. **Hypotension:** In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with MICARDIS. Either correct this condition prior to administration of MICARDIS, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia:** Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk. **Impaired Hepatic Function:** As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients. **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with MICARDIS. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS in patients with unilateral or bilateral renal artery stenosis but anticipate an effect similar to that seen with ACE inhibitors. **Dual Blockade of the Renin-Angiotensin-Aldosterone System:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function. The ONTARGET trial enrolled 25,620 patients ≥ 55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of MICARDIS and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of MICARDIS and ramipril is not recommended.

ADVERSE REACTIONS

The following adverse reaction is described elsewhere in labeling: Renal dysfunction upon use with ramipril. **Clinical Trials Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Hypertension:** MICARDIS has been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy. In placebo-controlled trials involving 1041 patients treated with various doses of MICARDIS (20–160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo. Adverse events occurring at an incidence of $\geq 1\%$ in patients treated with MICARDIS and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Table 1 Adverse Events Occurring at an Incidence of $\geq 1\%$ in Patients Treated with MICARDIS and at a Greater Rate Than in Patients Treated with placebo

	Telmisartan (n=1455) %	Placebo (n=380) %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of $\geq 1\%$ but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with MICARDIS tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials. The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%). In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with MICARDIS monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS tablets: **Autonomic Nervous System:** impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise; **Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; **Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; **Metabolic:** gout, hypercholesterolemia, diabetes mellitus; **Musculoskeletal:** arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness; **Resistance Mechanism:** infection, fungal infection, abscess, otitis media; **Respiratory:** asthma, bronchitis, rhinitis, dyspnea, epistaxis; **Skin:** dermatitis, rash, eczema, pruritus; **Urinary:** micturition frequency, cystitis; **Vascular:** cerebrovascular disorder; and **Special Senses:** abnormal vision, conjunctivitis, tinnitus, earache. During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated). **Clinical Laboratory Findings:** In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS tablets. Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia. Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen. Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function. **Cardiovascular Risk Reduction:** Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%). In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported. **Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of MICARDIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS. The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions. **Nursing Mothers:** It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of patients receiving MICARDIS in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Of the total number of patients receiving MICARDIS in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥ 65 to < 75 years of age was 42%; 15% of patients were ≥ 75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Insufficiency:** Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with MICARDIS tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Rx only



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