

# Beware the Liability Pitfalls of Electronic Records

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Contributing Writer

WASHINGTON — From a liability perspective, health information technology remains a double-edged sword whose parameters still need to be spelled out, experts maintained at a meeting sponsored by eHealth Initiative and Bridges to Excellence.

“It’s going to provide protection in some places and increase liability in others,”

said attorney Marcy Wilder, a partner with Hogan & Hartson.

When it comes to electronic clinical decision support (CDS) tools, Jud DeLoss, vice chair of the HIT Practice Group at the American Health Lawyers Association, recommended that physicians document their reasoning when they disregard the tool’s suggestion.

Although it would be “difficult to pull off,” attorneys could create a class of victims for whom they argue that clinical de-

cision support was not followed, leading to detrimental results, he said. Conversely, attorneys could charge that a physician overly relied on the tool “and did not actually engage in the care they said they did.”

Ms. Wilder pointed out another gray area created by HIT: delineating who contributed what sections to a patient’s electronic health record. “Look at the paper system,” she said. “We have handwriting and signatures, which are simple tools to identify who’s responsible for which clin-

ical applications, which provider made the diagnosis, who authorized the change in medication. It is both easier and more difficult to do that with electronic health records.”

The simplicity and efficacy of identity authentication “is going to depend upon the extent to which the vendors that are building the systems get this right,” she added.

Although systems are in place to address identity authentication in health care facilities, problems may arise when data from shared information warehouses such as a regional health information organization are incorporated into an electronic medical record, Ms. Wilder said. “That’s where it’s going to be very messy, and I think it will be a long time before we are going to be using shared data warehouses in part because of those kinds of liability issues.”

Physicians also are concerned about the validity of the portion of an electronic medical record that they did not make. Mr. DeLoss said the concern is that physicians might inadvertently end up becoming part of a malpractice suit by signing off on their portion of a medical record that also includes an entry by a physician who has a pending malpractice case.

Mr. DeLoss and Ms. Wilder added that as use of electronic medical records becomes more prevalent, physicians may have a duty to be familiar with a patient’s entire medical record if it is available. They also recommended that physicians spell out with hospitals via contracts which party is liable for problems that arise from software donated to them by hospitals.

## INDEX OF ADVERTISERS

<b>Amylin Pharmaceuticals, Inc.</b>	
Byetta	4a-4b
<b>Bayer HealthCare LLC</b>	
ALEVE	27
<b>Boehringer Ingelheim Pharmaceuticals, Inc.</b>	
Flomax	51-52
Spiriva	22, 32a-32b
<b>Cephalon, Inc.</b>	
Provigil	43-44
<b>Forest Laboratories, Inc.</b>	
Lexapro	24a-24b
Namenda	48a-48b
<b>Merck &amp; Co., Inc.</b>	
Zostavax	12a-12d
Januvia	36a-36b
<b>Novo Nordisk Inc.</b>	
NovoLog Mix 70/30	11-12
Levemir	23-24
<b>Pfizer Inc.</b>	
Lipitor	3-4
Aricept	19-20, 31-32
Detrol	34-36
Chantix	39-42
<b>Sanofi Pasteur</b>	
Adacel	20a-20b
<b>Santarus, Inc.</b>	
Zegerid	47-48
<b>Takeda Pharmaceuticals North America, Inc.</b>	
Amizta	7-8
Rozorem	28-30
ACTOplus met	52a-52b, 53
<b>Wyeth Pharmaceuticals Inc.</b>	
Enbrel	14-17
Effexor XR	44a-44d, 55-56

clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be informed about the importance of regular testing of renal function and hematologic parameters when receiving treatment with ACTOplus met.

Therapy with a thiazolidinedione, which is the active pioglitazone component of the ACTOplus met tablet, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOplus met. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Combination antihyperglycemic therapy may cause hypoglycemia. When initiating ACTOplus met, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

Patients should be told to take ACTOplus met as prescribed and instructed that any change in dosing should only be done if directed by their physician.

#### Drug Interactions: Pioglitazone HCl

*In vivo* drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.

#### Drug Interactions: Metformin HCl

**Furosemide:** A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood  $C_{max}$  by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the  $C_{max}$  and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

**Nifedipine:** A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin  $C_{max}$  and AUC by 20% and 9%, respectively and increased the amount excreted in the urine.  $T_{max}$  and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

**Cationic Drugs:** Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of ACTOplus met and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

**Other:** Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving ACTOplus met, the patient should be closely observed to maintain adequate glycemic control.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

**ACTOplus met**  
No animal studies have been conducted with ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

#### Pioglitazone HCl

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on  $mg/m^2$ ). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on  $mg/m^2$ ). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on  $mg/m^2$ ). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR  $\alpha/\gamma$  activity; however, pioglitazone is a selective agonist for PPAR $\gamma$ .

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with pioglitazone (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPR1), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on  $mg/m^2$ ).

#### Metformin HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times a human daily dose of 2000 mg of the metformin component of ACTOplus met based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no

tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin component of ACTOplus met based on body surface area comparisons.

#### Animal Toxicology

##### Pioglitazone HCl

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with the pioglitazone HCl component of ACTOplus met (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on  $mg/m^2$ ). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on  $mg/m^2$ ). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on  $mg/m^2$ ), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on  $mg/m^2$ ).

##### Pregnancy: Pregnancy Category C

##### ACTOplus met

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. ACTOplus met should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with ACTOplus met or its individual components. No animal studies have been conducted with the combined products in ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

##### Pioglitazone HCl

Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on  $mg/m^2$ , respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on  $mg/m^2$ ). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on  $mg/m^2$ ). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on  $mg/m^2$ ).

##### Metformin HCl

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times a human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

##### Nursing Mothers

No studies have been conducted with the combined components of ACTOplus met. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin is secreted in human milk. Because many drugs are excreted in human milk, ACTOplus met should not be administered to a breastfeeding woman. If ACTOplus met is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

##### Pediatric Use

Safety and effectiveness of ACTOplus met in pediatric patients have not been established.

##### Elderly Use

**Pioglitazone HCl:** Approximately 500 patients in placebo-controlled clinical trials of pioglitazone were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

##### Metformin HCl:

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, ACTOplus met should only be used in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS**). Because aging is associated with reduced renal function, ACTOplus met should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of ACTOplus met (see **WARNINGS**).

#### ADVERSE REACTIONS

The most common adverse events reported in at least 5% of patients in the controlled 16-week clinical trial between placebo plus metformin and pioglitazone 30 mg plus metformin were upper respiratory tract infection (15.6% and 15.5%), diarrhea (6.3% and 4.8%), combined edema/peripheral edema (2.5% and 6.0%) and headache (1.9% and 6.0%), respectively.

The incidence and type of adverse events reported in at least 5% of patients in any combined treatment group from the 24-week study comparing pioglitazone 30 mg plus metformin and pioglitazone 45 mg plus metformin are shown in Table 2; the rate of adverse events resulting in study discontinuation between the two treatment groups was 7.8% and 7.7%, respectively.

Table 2. Adverse Events That Occurred in  $\geq 5\%$  of Patients in Any Treatment Group During the 24-Week Study

Adverse Event Preferred Term	Pioglitazone 30 mg + metformin N=411 n (%)	Pioglitazone 45 mg + metformin N=416 n (%)
Upper Respiratory Tract Infection	51 (12.4)	56 (13.5)
Diarrhea	24 (5.8)	20 (4.8)
Nausea	24 (5.8)	15 (3.6)
Headache	19 (4.6)	22 (5.3)
Urinary Tract Infection	24 (5.8)	22 (5.3)
Sinusitis	18 (4.4)	21 (5.0)
Dizziness	22 (5.4)	20 (4.8)
Edema Lower Limb	12 (2.9)	47 (11.3)
Weight Increased	12 (2.9)	28 (6.7)

Most clinical adverse events were similar between groups treated with pioglitazone in combination with metformin and those treated with pioglitazone monotherapy. Other adverse events reported in at least 5% of patients in controlled clinical trials between placebo and pioglitazone monotherapy included myalgia (2.7% and 5.4%), tooth disorder (2.3% and 5.3%), diabetes mellitus aggravated (8.1% and 5.1%) and pharyngitis (0.8% and 5.1%), respectively.

In U.S. double-blind studies, anemia was reported in  $\leq 2\%$  of patients treated with pioglitazone plus metformin (see **PRECAUTIONS** section).

In monotherapy studies, edema was reported for 4.8% of patients treated with pioglitazone versus 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS** section).

#### Laboratory Abnormalities

**Hematologic:** Pioglitazone may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with pioglitazone appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and have rarely been associated with any significant hematologic clinical effects (see **PRECAUTIONS** section).

In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation (see **PRECAUTIONS** section).

**Serum Transaminase Levels:** During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with pioglitazone had ALT values  $\geq 3$  times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with pioglitazone, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with pioglitazone were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS** section).

**CPK Levels:** During required laboratory testing in clinical trials with pioglitazone, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive pioglitazone, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

#### OVERDOSAGE

##### Pioglitazone HCl

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

##### Metformin HCl

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected.

**INDICATIONS:** ACTOplus met is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

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