

CCHIT Releases First List of Certified EHRs

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The Certification Commission for Healthcare Information Technology has unveiled its first list of 20 ambulatory electronic health record products that meet its standards for functionality, interoperability, and security.

CCHIT was formed in 2004 by three leading health IT management and technology industry associations. It is under

contract to the federal government to develop certification criteria for EHRs and evaluate products. In this first round, CCHIT officials gave their seal of approval to 18 products that met all certification standards. Two additional products were given conditional premarket certification pending verification by users.

The certified products are designed to serve the spectrum of physician practices, Dr. Mark Leavitt, CCHIT chair, said during a press conference. Vendors whose prod-

ucts were certified received a CCHIT seal of approval that the product met 2006 standards, Dr. Leavitt said. That certification is good for up to 3 years or vendors can come back to CCHIT each year to be certified under the updated standards, he said.

This year's standards included some baseline interoperability functionality related to receiving lab results, but the bulk of the interoperability requirements will be applied starting next year, once standards have been harmonized, he said.

At the press conference, Health and Human Services Secretary Mike Leavitt announced HHS soon will publish a final rule creating safe harbors in federal antikickback statute and physician self-referral laws that would allow hospital systems and other large provider groups to donate health IT products to physicians in certain cases. The proposed rule was issued in October. ■

The list of certified products is available at www.cchit.org.

structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with AVANDAMET undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with AVANDAMET in all patients and periodically thereafter per the clinical judgement of the healthcare professional. Therapy with AVANDAMET should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDAMET should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDAMET in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDAMET, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDAMET should be discontinued. AVANDAMET should not be used in patients who experienced jaundice while taking troglitazone. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. If jaundice is observed, drug therapy should be discontinued. In addition, if the presence of hepatic disease or hepatic dysfunction of sufficient magnitude to predispose to lactic acidosis is confirmed, therapy with AVANDAMET should be discontinued. There are no data available from clinical trials to evaluate the safety of AVANDAMET in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. AVANDAMET should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests: Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response. Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDAMET in all patients and periodically thereafter (see PRECAUTIONS, Hepatic Effects and ADVERSE REACTIONS, Laboratory Abnormalities, Serum Transaminase Levels). Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B₁₂ deficiency should be excluded.

Information for Patients: Patients should be informed of the potential risks and advantages of AVANDAMET and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, weight loss, and a regular exercise program because these methods help improve insulin sensitivity. The importance of regular testing of blood glucose, glycosylated hemoglobin (HbA1c), renal function, and hematologic parameters should be emphasized. Patients should be advised that AVANDAMET can begin to take effect 1 to 2 weeks after initiation, however it can take 2 to 3 months to see the full effect of glycemic improvement. The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue AVANDAMET immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving AVANDAMET. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDAMET should immediately report these symptoms to their physician. Therapy with AVANDAMET, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDAMET (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions: An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. Although drug interactions with cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of AVANDAMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. When drugs that produce hyperglycemia which may lead to loss of glycemic control are administered to a patient receiving AVANDAMET, the patient should be closely observed to maintain adequate glycemic control. (See CLINICAL PHARMACOLOGY, Drug Interactions in full prescribing information.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal studies have been conducted with the combined products in AVANDAMET. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone maleate: Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue. Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation. Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrus cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose of rosiglitazone). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Metformin Hydrochloride: 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 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg of the metformin component of AVANDAMET 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 3 times the maximum recommended human daily dose of the metformin component of AVANDAMET based on body surface area comparisons.

Animal Toxicology: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy: Pregnancy Category C: 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 monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. AVANDAMET 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 AVANDAMET or its individual components. No animal studies have been conducted with the combined products in AVANDAMET. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone maleate: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of AVANDAMET. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Metformin hydrochloride: Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Labor and Delivery: The effect of AVANDAMET or its components on labor and delivery in humans is unknown.

Nursing Mothers: No studies have been conducted with the combined components of AVANDAMET. In studies performed with the individual components, both rosiglitazone-related material and metformin were detectable in milk from lactating rats. It is not known whether rosiglitazone and/or metformin is excreted in human milk. Because many drugs are excreted in human milk, AVANDAMET should not be administered to a nursing woman. If AVANDAMET is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Rosiglitazone maleate: After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m², were randomized to treatment with 2 mg twice daily of rosiglitazone (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, fasting plasma glucose (FPG) decreased in patients naive to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of rosiglitazone-treated patients and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naive to therapy with anti-diabetic drugs and for patients previously treated with anti-diabetic therapy.

Week 24 FPG and HbA1c Change from Baseline Last-Observation-Carried Forward in Children with Baseline HbA1c >6.5%

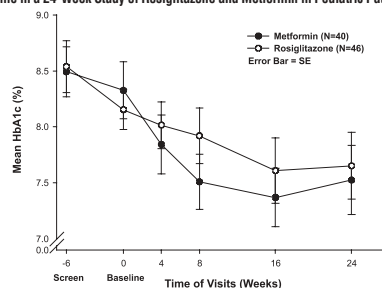
	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
N	40	45	43	32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted Treatment Difference* (rosiglitazone-metformin) [†]		8		21
(95% CI)		(-15, 30)		(-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted Treatment Difference* (rosiglitazone-metformin) [†]		0.2		0.5
(95% CI)		(-0.6, 0.9)		(-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

* Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

[†] Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of rosiglitazone and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin (see PRECAUTIONS, Rosiglitazone maleate, Weight Gain). Fifty four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study. Adverse events observed in this study are described in ADVERSE REACTIONS, Pediatric.

Mean HbA1c Over Time in a 24-Week Study of Rosiglitazone and Metformin in Pediatric Patients — Drug-Naïve Subgroup



Geriatric Use: 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, AVANDAMET should only be used in patients with normal renal function (see CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY, Pharmacokinetics in complete prescribing information). Because reduced renal function is associated with increasing age, AVANDAMET should be used with caution in elderly patients. 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 AVANDAMET (see also WARNINGS and DOSAGE AND ADMINISTRATION in complete prescribing information).

ADVERSE REACTIONS: Adult: The incidence and types of adverse events reported in a controlled, 32-week double-blind clinical trial of AVANDAMET as initial therapy (n = 468) are shown below.

Adverse Events (>5% in Any Treatment Group) Reported by Patients in a 32-week Double-blind Clinical Trial of AVANDAMET as Initial Therapy

	AVANDAMET N = 155	Metformin N = 154	Rosiglitazone N = 159
Preferred term	%	%	%
Nausea/vomiting	16	13	8
Diarrhea	14	21	7
Headache	11	12	10
Dyspepsia	10	8	9
Upper respiratory tract infection	9	7	8
Dizziness	8	3	5
Edema	6	3	7
Nasopharyngitis	6	5	4
Abdominal pain	5	6	7
Arthralgia	5	3	7
Loose Stools	5	6	1
Constipation	5	4	6
Influenza	1	2	6

The incidence and types of adverse events reported in controlled, 26-week clinical trials of rosiglitazone maleate administered as second-line therapy in combination with metformin hydrochloride 2,500 mg/day are shown below, in comparison to adverse reactions reported in association with rosiglitazone and metformin monotherapies.

Adverse Events (≤5% in Any Treatment Group) Reported by Patients in 26-week Double-blind Clinical Trials of Rosiglitazone Added to Metformin as Second-Line Therapy

	Rosiglitazone N = 2,526	Placebo N = 601	Metformin N = 225	Rosiglitazone plus metformin N = 338
Preferred term	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	16.0
Injury	7.6	4.3	7.6	8.0
Headache	5.9	5.0	8.9	6.5
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	2.1
Fatigue	3.6	5.0	4.0	5.9
Sinusitis	3.2	4.5	5.3	6.2
Diarrhea	2.3	3.3	15.6	12.7
Viral infection	3.2	4.0	3.6	5.0
Arthralgia	3.0	4.0	2.2	5.0
Anemia	1.9	0.7	2.2	7.1

In the double-blind trial evaluating AVANDAMET as initial therapy, mild (no intervention required) to moderate (minor intervention required) symptomatic hypoglycemia was reported by 18/155 (12%) of patients treated with AVANDAMET, 14/154 (9%) with metformin, and 13/159 (8%) with rosiglitazone. Approximately half of these episodes were accompanied by a simultaneous capillary glucose measurement, and the rate of confirmed hypoglycemia (blood glucose ≤50mg/dL) was low in this clinical study: 0.6% (1/155) for AVANDAMET, 1.3% (2/154) for metformin and 0% with rosiglitazone. No hypoglycemic episode led to withdrawal with AVANDAMET treatment, and no patients required medical intervention due to hypoglycemia.