### WHO Seeks to Standardize Clinical Trial Registries

BY KERRI WACHTER Senior Writer

he World Health Organization has launched a major initiative to standardize the way information on clinical trials is made available to the public.

In an attempt to address growing public concerns about the transparency of medical research involving human participants, the World Health Organization is recommending 20 key details that all clinical trial registries should include.

"Registration of all clinical trials and full disclosure of key information at the time of registration are fundamental to ensuring transparency in medical research and fulfilling ethical responsibilities to patients and study participants," Dr. Timothy Evans, assistant directorgeneral of the World Health Organization, said in a statement.

WHO's International Clinical Trials Registry Platform is not itself a registry,

Rx only

but instead provides standards for all clinical trial registries. These standards require inclusion of information about the following: sources of monetary or material support, primary and secondary sponsors, contacts for public and scientific queries, countries of recruitment, health conditions or problems studied, interventions, key inclusion and exclusion criteria, study design, date of first enrollment, target sample size, recruitment status, and primary and secondary outcomes.

#### **Diovan HCT®**

valsartan and hydrochlorothiazide, USP Combination Tablets 80 mg/12.5 mg; 160 mg/12.5 mg; 160 mg/25 mg; 320 mg/12.5 mg; 320 mg/25 mg BRIEF SUMMARY: Please see package insert for full prescribing information

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-anglotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan HCT should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

NDICATIONS AND USAGE: Diovan HCT® (valsartan and hydrochlorothiazide, USP) is indicated for the treatment of hypertension This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION in the full prescribing

CONTRAINDICATIONS: Diovan HCT<sup>®</sup> (valsartan and hydrochlorothiazide, USP) is contraindicated in patients who are hyper-sensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

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nbryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester med. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the

should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of Diovan HCT as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system 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 intraamindic environment. If oligothydramnios is observed, Diovan HCT should be discontinued unless it is considered life-saving for the mother. Con-traction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be avare, however, that oligothydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in ultere* exposure to an angiotensin II receptor antagonist should be closely observed for hypoten-sion, 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 means of reversing hypotension and/or substituting for dis-ordered renal function.

ordered renal function. Valsartan - Hydrochlorothiazide in Animats: There was no evidence of teratogenicity in mice, rats, or rabbits treated orally with valsartan at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 188, 31 and 3 mg/kg/day. These non-teratogenic doses in mice, rats and rabbits, respectively, regresent 9, 35 and 05 times the maximum recommended human dose (MRHD) of valsartan and 38, 13 and 2 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide ad a 60-Kg patient.)

The maximum recommended human dose (MRHD) of valastran and 38, 13 and 2 times the MRHD of hydrochlorothiazide on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-45 patient.)
 Feltotoxichy was observed in association with maternal toxichly in rats and rabbits at valsartan doses of 2-200 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of 2-63 and 3 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of 2-63 and 3 mg/kg/day, respectively, in combination wolf hydrochlorothiazide doses of 1-63 and 3 mg/kg/day, respectively, in combination on observed adverse effect doses in mice, rats and rabbits for valsartan were 600. 100 and 3 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of 186, 31 and 1 mg/kg/day. These no adverse effect doses in mice, rats and rabbits, respectively, in combination with bg/mg/day, respectively, in combination with hydrochlorothiazide on 40 - 18 times the MRHD of hydrochlorothiazide on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide on 40 - kg patient.)
 Valsartan in Animals: No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 10 mg/kg/day. However, significant decreases in feal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which garental rats were treated with valsartan at oral, maternally toxic (reduction in body weight) soberved in studies of 320 mg/kg/day. Then oobserved adverse effect doses of 600 mg/kg/day, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 5 and 10 mg/kg/day. Then oobserved adverse of the dational Toxicology Program, pregnant mice and rats that received hydrochlorothiazide duited bases of 1000 mg/kg/day, respectivel

PRECAUTIONS: Serum Electrolytes: Valsartan - Hydrochlorothiazide: In the controlled trials of various doses of the combi-nation of valsartan and hydrochlorothiazide in incidence of hypertensive patients who developed hypokalemia (serum potas sium -3.5 mEq.1) was 3.0%; the incidence of hyperkalemia (serum potassium -5.7 mEq.1) was 0.4%.

Lithium). PRECAUTIONS: Serum Electrolytes: Valsartan - Hydrochlorothiazide: In the controlled trials of various doses of the combi-nation of valsartan and hydrochlorothiazide the incidence of hypertansive patients who developed hypokalemia (serum potas-sium <3.5 mEqL) was 3.0%; the incidence of hyperkalemia (serum potassium >5.7 mEqL) was 0.4%. In controlled clinical trials of Diovan HCT® (valsartan and hydrochlorothiazide, USP), the average change in serum potassium was near zero in subjects who received Diovan HCT® 160/12.5 mg, 320/12.5 mg or 320/25 mg but the average subject who received Diovan HCT® 01.25 mg, 80/25 mg or 160/25 mg experienced a mild reduction in serum potassium. In clinical trials, the opposite effects of valsartan (80, 160 or 320 mg) and hydrochlorothiazide (12.5 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to delect possible electrolyte imbalance should be performed at appropriate intervals. Hydrochlorothiazde: All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethary, drowsiness, reetlesness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oigura, tachycardia, and gastrointestinal disturbances such as nause and vomitin, Hypokalemin amy develop, especial the response of the hard to the toxie effects of digitalis (e.g., incrased ventricular arrhythina and may also sensitize or exaggreat the response of the hard to the toxie effects of digitalis (e.g., incrased ventricular arrhythina and may also sensitize or exaggreat the response of the hypokalemia Hypokalemia, in acuta sait deletion, appropriate replacement may occur in edentalous patients in hot weather, appropriate therapy is water restriction, rather than administration of sait except in rare instances when the hyponatemia is ma

severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar out-comes have been reported with Diovan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or biod urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral or bilateral renal artery stenosis, so significant increases in serum creatinine or biod urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral or bilateral renal artery stenosis, so significant increases in serum creatinine or biod urea nitrogen have observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, so should be anticipated. *Hyatochtorthaizide*: Thizides should be used with caution in severe renal feases. In patients with renal disease, thizides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Information for Patients: *Prepanaey*: Formale patients of childbearing age should be told bout the consequences of second- and third-trimester exposure to drugs that at on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be eactioned that lightheadedness can occur, especially during the first during and that should be reported to the prescribing physician. The patients should be told that if syncope occurs, Diovan HCT should be reported to the prescribing physician. The patients should be cautioned that ingentees real index to be cautioned that ingentees and on possible syncope. *Potassium Supplements:* A patient receiving Diovan HCT should be told that the or should be cautioned to not to use potassium supplements or sait substitutes containing potassium winnout consulting the prescriptioning physician. Drug Interactions: Valardara: No clinically significant pharmacokinetic interactions were observed when valastant was coad-ministered with amoldipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more that atenolo alone. Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan metabolism have not been identified but do not seem to be CYP 450 inscriptions. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is

atenolo alone. Coadministration of valsartan and wartarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of wartarin. *CPP 450 Instactions:* The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on the CYP 450 is also unknown. *Hydrochlorabhazide:* When administered concurrently the following drugs may interact with thiazide diuretics: *Alcohol, barbi-turates, or narcotics - Potentiation of orthostatic hypotension may occur. Antidiabetic drugs (oral agents and insulin) - Dosage adjustment of the antidiabetic drug may be required. <i>Other antihypetensive drugs* - Additive effect or potentiation. *Cholestyra-mine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.* Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption, *Promstein the* passibul *Pressor amines* (e.g., norepinently) be given with diverses. Diructica gents reduce the renal clearance of lithium and ada high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Divan HCT. *More-steroida anti-inflammatory drugs* - In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretis:. Therefore, when Divan HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Valsartan** an Mydrochlorothiazide. However, these studies have been conducted for valsartan as well as hydrochlorothiazide alone. Based on the preclinical safety and human parmacokinetic stud-les, there is no indication of any doverse interaction between

Nursing Mothers: It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lac-tating rats. Thiażides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the

Should be made whether to discontinue nursing of 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.

Gerlatric Use: In the controlled clinical trials of Diovan HCT, 764 (17.5%) of patients treated with valsartan-hydrochlorothiazide were ≥65 years and 118 (2.7%) were ≥75 years. No overall difference in the efficacy or safety of valsartan-hydrochlorothiazide were ≥65 years and 118 (2.7%) were ≥75 years. No overall difference in the efficacy or safety of valsartan-hydrochlorothiazide were ≥65 years and 118 (2.7%) were ≥75 years. No overall difference in the efficacy or safety of valsartan-hydrochlorothiazide. DVERSE REACTIONS: Diovan HCT® (valsartan and hydrochlorothiazide. USP) has been evaluated for safety in more than 5700 patients, including over 990 treated for over 6 months, and over 370 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infreguently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan HCT was comparable to placebo. The overall frequency of adverse experiences was neither obser-related to genete, age or race. In controlled clinical trials, discontinuation of therapy. The overall incidence of adverse experiences with Diovan HCT were headche and dizenses. The only adverse experience that occurred in controlled clinical trials in at least 2% of patients treated with Diovan HCT and at a higher incidence in valsartan-hydrochlorothiazide (>2.4% vs 1.9%). Dose-related of horotatic effects were seen in fewer than 1% of patients. In individual trials, a dose-related increase in the incidence of dizziness was observed in patients treaded with Diovan HCT. Other adverse experiences that have been reported with valsartan-hydrochlorothiazide (>2.2% of valsartan-hydrochlorothiazide (>2.4% vs 1.9%). Dose-related of horosatide effects were seen in fatulence, dny mouth, nausea, abdomi

postural, paraesthesia, and somnolence. *Psychiatric* Anxiety and insomnia. *Renal and Urinary:* Pollakiuma. *Begriatory*. Thoracic and *Medisatinai:* Dysnew, acough, nasa congestion, pharyngolaryngeal pain and sinus congestion. *Skin and Subcutaneous Tissue:* Hyperhidrosis and rash. *Vascular.* Hypotension, pharyngolaryngeal pain and sinus congestion. *Skin and Subcutaneous Tissue:* Hyperhidrosis and rash. *Vascular.* Hypotension, Other reported events seen less frequently in clinical trials included abnormal vision, anaphylaxis, bronchospasm, constipa-tion, depression, debrydration, decreased libido, dysuria, epistaxis, flushing, gout, increased appetite, muscle weakness, pharynglits, puritus, sunburn, syncope, and viral infection. *Valsartari.* It trials in which valsartara was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartara. It childer a dat dry cough when they had previously received ACE inhibitors with or received valsartara, hydrochiorthizide, or lisinopril were 20%, 19%, 69%, respectively (p. <0.001).

In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, hydrochlorothiazide, or lisinopil were 20%, 19%, 69%, respectively (p. 0.001). Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angloedema. **Post-Marketing Experience:** The following additional adverse reactions have been reported in post-marketing experience: **The following additional adverse reactions have been reported in post-marketing experience: The following additional adverse reactions have been reported in post-marketing experience: The following additional adverse reactions have been reported in patients receiving angiotensin II receiptor blockers. Hydrochlorothiazide:** Other adverse ease of rhabdomyol-ysis have been reported in patients receiving angiotensin II receiptor blockers. Hydrochlorothiazide: Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below: **Body RS Muble:** weakness; **aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; Hypersensitivity: puru, photosensitivity, urticaria, neorotizing angilisti (susculitis and cutaneous vasculitis), Itever repriratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; <b>Metabolic:** hyperglycemia, glycosuria, hyperuricemia; **Musculosteleta**!: muscle spasm, **Nervous System/Psychiatri:** resilessness; **Rena**!: renal failure, renal dyslunction, interstitian heprihus; **Suin:** erythema multiforme including Stevens-Johnson syndrome, extoliative dermatitis including tokic epiderma hercolysis; **Special Senses:** transient blurred vision, xanthopsia. **Clinical Laboratory Test Findings:** In controlled clinical trials, clinical lubarator **Mitrogen (BUM):** Minor elevations in creatinine and BUN occurred in 15% or posterively, of patients taing Diovan HCT and 0.4% and **6**%, respectively, given

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The voluntary initiative is part of a growing movement toward greater accessibility to clinical trial information, prompted in part by high-profile cases involving the suppression of data by pharmaceutical companies.

In the European Union, all clinical trials conducted in member states are required to be registered in the EudraCT database, supervised by the European Medicines Agency. In the United States, www.ClinicalTrials.gov (developed and run by the National Institutes of Health) enrolls publicly and privately funded clinical trials worldwide.

However, there are several hundred other national and private clinical trial registries located around the world. The Registry Platform seeks to bring participating registries together in a global network to provide a single point of access to the information stored in them, according to a World Health Organization statement.

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The World Health Organization has acknowledged the need to balance increased transparency with the protection of competitive advantage, and it appears that this issue may come down to a question of the timing of disclosure.

In comments submitted to a World Health Organization formal consultation on disclosure timing policy in April, the Pharmaceutical Research and Manufacturers of America noted "there may be infrequent instances where companies may regard certain data elements as sensitive for competitive reasons and wish to delay public disclosure."

In particular, the organization said that

companies may wish to delay the disclosure of the official scientific title of the study, specific mechanism or molecular identifiers of the intervention, target sample size, primary outcome, and key secondary outcomes.

The WHO Registry Platform is expected to launch a Web-based search portal later this year. This search portal would allow interested individuals to search among participating registries for clinical trials taking place or completed throughout the world.

For more information on the WHO Registry Platform, visit www.who.int/ictrp/en.



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