

AHA Guidelines Released on Stroke in Children

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The first comprehensive guidelines for the diagnosis and management of stroke in children are intended to provide a wide range of clinicians responsible for treating cerebrovascular disease in infants and children with evidence- and consensus-based recommendations, according to the American Heart Association. "Management of Stroke in Infants and

Children," written by a group of experts from the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young, was recently released online.

"Only a few centers in the country have a high level of expertise in dealing with stroke in children, and these guidelines share this concentrated knowledge with physicians who don't have access to that expertise," committee chair E. Steve Roach said in an interview.

One important message of the statement is that stroke in children is much more common than is generally realized. Data from the National Hospital Discharge Survey from 1980 to 1998 suggested that the overall risk of stroke from birth through 18 years is 13.5/100,000 and that the rate of hemorrhagic stroke for term infants is 6.7/100,000 per year. Other recent investigations found that neonatal stroke occurs in about 1 in 4,000 live births, with about 80% being ischemic.

Strokes in children differ from those in adults, in that few are associated with atherosclerosis. One similarity, however, is that in both adults and children once the stroke has occurred, no medicine can reverse it, said Dr. Roach, chief of neurology at Nationwide Children's Hospital and professor of pediatric neurology, Ohio State University, both in Columbus.

"However, an aggressive approach to finding out the cause of the stroke is your best chance for preventing stroke No. 2 or 3 and preventing the cumulative pileup of brain damage that will determine whether that child grows into a normally functioning adult," he said.

Among the causes and risk factors for stroke in infants and children discussed in the statement are sickle cell disease, congenital heart disease, and cervicocephalic arterial dissection (Circulation 2008 [doi:10.1161/strokeaha.108.189696]). For sickle cell disease, detailed recommendations are included on primary and secondary stroke prevention.

Management of acute ischemic stroke should include optimal hydration and correction of hypoxemia and hypotension. Periodic transfusions are recommended for children aged 2-16 years with abnormal transcranial Doppler findings, and those with a confirmed cerebral infarction should be on a program of red cell transfusion with measures to prevent iron overload.

For hemorrhagic stroke, recommendations include noninvasive testing and standard cerebral angiography if needed, along with stabilizing measures such as controlling hypertension and seizures and managing increased intracranial pressure. Surgical evacuation of a supratentorial intracerebral hematoma is not recommended in most circumstances, although in certain selected patients with developing brain herniation or very high intracranial pressure, surgery may be helpful.

With cerebral venous sinus thrombosis (CVST) in children, anticoagulation is reasonable, with the exception of neonates. "Until there is more evidence of safety and effectiveness, anticoagulation is not appropriate for most neonates with CVST," the authors wrote.

Some recommendations are likely to cause controversy, according to Dr. Heather J. Fullerton, who directs the pediatric stroke and cerebrovascular disease center at the University of California, San Francisco. "For example, the guidelines recommend anticoagulation only for neonates who have some evidence of progression of venous sinus thrombosis, either radiographically or clinically, whereas in many institutions neonates with venous sinus thrombosis are routinely anticoagulated," she said in an interview.

Nonetheless, "these are landmark comprehensive guidelines," said Dr. Fullerton, who was not a member of the writing group.

"These guidelines will be helpful in that they express the consensus opinion of a group of experts based on the existing literature and will be extremely useful for clinicians who have struggled with how to manage these patients in the absence of more evidence," she said.

LETAIRIS® (ambrisentan) 5 mg and 10 mg Tablets

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WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations $>3\times$ ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations $>3\times$ ULN has been accompanied by bilirubin elevations $>2\times$ ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly. In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment. Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases ($>3\times$ ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $>2\times$ ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals [see Contraindications (4.1)]. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests. Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP [see WARNINGS, Prescribing and Distribution Program for LETAIRIS].

INDICATIONS AND USAGE: LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

DOSAGE AND ADMINISTRATION: Adult Dosage: Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). Liver function tests should be measured prior to initiation and during treatment with LETAIRIS [see Warnings and Precautions (5.1)]. **Women of Childbearing Potential:** Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS [see Contraindications (4.1)]. **Pre-existing Hepatic Impairment:** LETAIRIS is not recommended in patients with moderate or severe hepatic impairment [see Special Populations (8.7)].

CONTRAINDICATIONS: Pregnancy Category X: Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women. LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS: Potential Liver Injury (see BOXED WARNING): Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3-times the upper limit of normal ($>3\times$ ULN) and total bilirubin $>2\times$ ULN is a marker for potentially serious hepatic injury. Liver function tests were closely monitored in all clinical studies with LETAIRIS. For all LETAIRIS-treated patients (N=483), the 12-week incidence of aminotransferases $>3\times$ ULN was 0.8% and $>8\times$ ULN was 0.2%. Liver chemistries must be measured prior to initiation of LETAIRIS and at least every month thereafter. If there are aminotransferase elevations $>3\times$ ULN and $\leq 5\times$ ULN, they should be re-measured. If the confirmed level is $>3\times$ ULN and $\leq 5\times$ ULN, reduce the daily dose or interrupt treatment and continue to monitor every two weeks until the levels are $<3\times$ ULN. If there are aminotransferase elevations $>5\times$ ULN and $\leq 8\times$ ULN, LETAIRIS should be discontinued and monitoring should continue until the levels are $<3\times$ ULN. LETAIRIS can then be re-initiated with more frequent measurement of aminotransferase levels. If there are aminotransferase elevations $>8\times$ ULN, treatment should be stopped and re-initiation should not be considered. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin $>2\times$ ULN, LETAIRIS treatment should be stopped. **Hematological Changes:** Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETAIRIS in the 12-week placebo-controlled studies was 0.8 g/dL. Marked decreases in hemoglobin ($>15\%$ decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving LETAIRIS (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at one month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered. **Peripheral Edema:** Peripheral edema is a known class effect of endothelin receptor antagonists. In addition, there have been post-marketing reports of fluid retention occurring within weeks after starting LETAIRIS which required intervention with a diuretic, fluid management, and, in some cases, hospitalization for decompensating heart failure. **Co-administration of LETAIRIS and Cyclosporine A:** Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), Organic Anion Transport Protein (OATP), and CYP3A4. *In vitro* data indicate ambrisentan is a substrate of P-gp, OATP and CYP3A. Therefore, use caution when LETAIRIS is co-administered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS [see Drug Interactions (7)]. **Co-administration of LETAIRIS and Strong CYP3A and 2C19 Inhibitors:** Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) and CYP2C19-inhibitors (e.g., omeprazole) [see Drug Interactions (7)]. **Prescribing and Distribution Program for LETAIRIS:** Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition,

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ADVERSE REACTIONS: Clinical Trials Experience: Safety data for LETAIRIS were obtained from two 12-week, placebo-controlled studies in patients with PAH (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year). In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse events that occurred in $>3\%$ of the patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

Table 1 Adverse Events in $>3\%$ of PAH Patients Receiving LETAIRIS and More Frequent than Placebo

Adverse event	LETAIRIS (N=261)	
	Placebo (N=132)	n (%)
Peripheral edema	14 (11)	45 (17)
Nasal congestion	2 (2)	15 (6)
Sinusitis	0 (0)	8 (3)
Flushing	1 (1)	10 (4)
Palpitations	3 (2)	12 (5)
Nasopharyngitis	1 (1)	9 (3)
Abdominal pain	1 (1)	8 (3)
Constipation	2 (2)	10 (4)
Dyspnea	4 (3)	11 (4)
Headache	18 (14)	38 (15)

Note: This table includes all adverse events $>3\%$ incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of $\geq 1\%$ between the LETAIRIS and placebo groups.

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Fewer patients receiving LETAIRIS had adverse events related to liver function tests compared to placebo. Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥ 65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28).

DRUG INTERACTIONS: The drug interaction potential of ambrisentan is not well characterized because *in vivo* drug interaction studies were not conducted with the following types of drugs: strong inhibitors of CYP3A4 (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), and CYP2C19 (omeprazole), strong inducers of CYP3A and 2C19 (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin); and inducers of CYPs, UGTs and P-gp (rifampin). The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown. **Cyclosporine A:** Use caution when LETAIRIS is co-administered with cyclosporine A [see Warnings and Precautions (5.4)]. **Strong CYP3A or 2C19 Inhibitors:** Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole) [see Warnings and Precautions (5.5)]. **Inducers of P-gp, CYPs, and UGTs:** Use caution when LETAIRIS is co-administered with inducers of P-gp, CYPs, and UGTs. **Warfarin:** In healthy volunteers receiving warfarin, daily doses of LETAIRIS (10 mg once daily) did not have a clinically significant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate). In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of LETAIRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose. **Sildenafil:** In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of LETAIRIS (10 mg once daily) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of LETAIRIS (10 mg).

USE IN SPECIFIC POPULATIONS: Nursing Mothers: It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. **Pediatric Use:** Safety and effectiveness of LETAIRIS in pediatric patients have not been established. **Geriatric Use:** In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥ 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan [see Clinical Pharmacology (12.3)]. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. **Hepatic Impairment:** LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. Use caution when administering LETAIRIS to patients with mild pre-existing impaired liver function who may require reduced doses of LETAIRIS [see Dosage and Administration (2.3)].

NONCLINICAL TOXICOLOGY: Impairment of Fertility: The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Effects on sperm count, sperm morphology, mating performance and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). There are insufficient data on the effects of ambrisentan or other endothelin receptor antagonists on testicular function in man.

INFORMATION FOR PATIENTS: Importance of Preventing Pregnancy: Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test. Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one primary form simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. **Adverse Liver Effects:** Patients should be advised of the importance of monthly liver function testing and instructed to immediately report any symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) to their physician.

GS22-081-001

For detailed information, please see full prescribing information.

To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com.

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