

# AAP: Kids Should Avoid Energy and Sports Drinks

BY MICHELE G. SULLIVAN

FROM PEDIATRICS

**E**nergy drinks have no place in a young person's diet, and sport drinks are useful only to student athletes who engage in prolonged, rigorous activity, according to a clinical report issued by the American Academy of Pediatrics.

Water should be encouraged as the

principal source of hydration for children and adolescents, the report concluded.

Too many children and adolescents consume both types of drinks without any knowledge of their potentially deleterious health effects (Pediatrics 2011;127:1182-9). Carbohydrates and caffeine are the chief concerns in the beverages, according to the report.

"The total amount of caffeine contained in some cans or bottles of energy

drinks can exceed 500 mg – equivalent to 14 cans of common caffeinated soft drinks – and is clearly high enough to result in caffeine toxicity. A lethal dose of caffeine is considered to be 200-400 mg/kg," lead authors Dr. Marcie B. Schneider of Greenwich, Conn., and Dr. Holly J. Benjamin of the University of Chicago wrote on behalf of the academy.

Marketing of these products aims to convince young people that sports drinks

containing electrolytes and carbohydrates are superior to water for hydration during exercise. Companies also advertise energy drinks as a providing a healthy boost to physical and mental energy in children and teens. Neither claim is accurate, according to the report.

In assessing the composition of these drinks and their potential health effects, the authors reviewed literature published from 2000 through 2009. They concluded that carbohydrates are the chief concern in sports drinks.

The average sports beverage contains 2-19 grams of carbohydrate, yielding up to 270 calories per serving. "This excessive caloric intake can substantially increase the risk for overweight and obesity in children and adolescents and should be avoided." Sports drinks are also often highly acidic, with a pH of 3-4.

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Proponents of sports drinks tout the electrolyte, vitamin, and mineral content as beneficial. Young people should be taught that water is the best beverage before, during, and after exercise. Even "muscle recovery" sports drinks, which contain forms of protein, are not really beneficial. "Heavily marketed effects of specific amino acids in sports drinks have not been supported by appropriate clinical trials," according to the report.

While sports drinks may simply be unhelpful sources of added calories, energy drinks may actually be dangerous if consumed in large quantities, they said. Caffeine is molecularly similar to adenosine and can replace it in cell receptors. "The effects of caffeine on various organ systems include increases in heart rate, blood pressure, speech rate, motor activity, attentiveness, gastric secretion, diuresis, and temperature," the report stated.

The American Association of Poison Control Centers confirms these findings. In 2005, the association reported that its centers had fielded more than 4,600 calls about caffeine. "Of these calls, 2,600 included patients younger than 19 years, and 2,345 patients required treatment, although the number of pediatric patients who required treatment was not defined," according to the report.

Energy drinks may also contain other stimulants touted as "natural," including guarana, a plant extract that itself contains caffeine. "The presence of guarana in an energy drink is a cause for concern, because it increases the total caffeine level in the beverage," according to the report.

All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. ■

## ONGLYZA™ (saxagliptin) tablets

Rx ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

### INDICATIONS AND USAGE

#### Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. [See *Clinical Studies (14)* in Full Prescribing Information.]

#### Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

#### Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA. [See *Adverse Reactions*.]

#### Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

### ADVERSE REACTIONS

#### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Monotherapy and Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

**Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials\* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo**

|                                   | Number (%) of Patients |                  |
|-----------------------------------|------------------------|------------------|
|                                   | ONGLYZA 5 mg<br>N=882  | Placebo<br>N=799 |
| Upper respiratory tract infection | 68 (7.7)               | 61 (7.6)         |
| Urinary tract infection           | 60 (6.8)               | 49 (6.1)         |
| Headache                          | 57 (6.5)               | 47 (5.9)         |

\* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

#### Use in Renal Impairment

ONGLYZA 2.5 mg was compared to placebo in a 12-week trial in 170 patients with type 2 diabetes and moderate or severe renal impairment or end-stage renal disease (ESRD). The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo.

#### Adverse Reactions Associated with ONGLYZA Coadministered with Metformin in Treatment-Naïve Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naïve patients.

**Table 2: Initial Therapy with Combination of ONGLYZA (saxagliptin) and Metformin in Treatment-Naïve Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)**

|                 | Number (%) of Patients             |                     |
|-----------------|------------------------------------|---------------------|
|                 | ONGLYZA 5 mg + Metformin*<br>N=320 | Metformin*<br>N=328 |
| Headache        | 24 (7.5)                           | 17 (5.2)            |
| Nasopharyngitis | 22 (6.9)                           | 13 (4.0)            |

\* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

#### Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6% versus placebo (10.1%)). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naïve patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

In the active-controlled trial comparing add-on therapy with ONGLYZA 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with ONGLYZA 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) ( $p < 0.0001$ ).

During 12 weeks of treatment in patients with moderate or severe renal impairment or ESRD, the overall incidence of reported hypoglycemia was 20% among patients treated with ONGLYZA 2.5 mg and 22% among patients treated with placebo. Four ONGLYZA-treated patients (4.7%) and three placebo-treated patients (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

#### Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

#### Infections

In the unblinded, controlled, clinical trial database for saxagliptin to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 saxagliptin-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with saxagliptin use. Causality has not been estimated and there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. There have been no spontaneous reports of opportunistic infections associated with saxagliptin use.

#### Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

#### Laboratory Tests

##### Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microl, mean decreases of approximately 100 and 120 cells/microl with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microl was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

##### Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

### DRUG INTERACTIONS

#### Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole,

nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA (saxagliptin) should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.]

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

##### Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the MRHD (saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, morbidity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hip.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

#### Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

#### Pediatric Use

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

#### Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.]

#### OVERDOSAGE

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

#### PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

#### Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

#### Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

Manufactured by:

**Bristol-Myers Squibb**  
Princeton, NJ 08543 USA

Marketed by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543  
and  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

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