



DEBRA R. COUNTS, M.D.

**G**rowth is a terrific biomarker for general health, and a slowing of growth may be a sign of underlying disease. So which children deserve an evaluation?

Short stature is defined as growth below the third percentile. In addition to these children, a child who is crossing one percentile line on the growth chart also deserves evaluation. The sole exception is an otherwise healthy child developing well who may, in the second year of life, adjust to genetics (for example, a big baby born to short parents).

The key is to identify the short child by monitoring the growth pattern, evaluating him to find a specific diagnosis, and then targeting the clinical intervention.

Consistent measurement of a child's height at every health care encounter is the most important strategy to identify a child with short stature. Some children do not go for regular well-child visits

**The key is to identify the short child by monitoring the growth pattern, evaluating him to find a specific diagnosis, and then targeting the clinical intervention.**

once they have most of their immunizations completed and may show up for sick visits only. In many cases, only weight but not height is measured during these acute care visits. For example, in my pediatric endocrinology practice, it is not unusual to see children who are 12 years old without a height measurement for the previous 7 years because the family did not present to the primary care physician for well care.

The benefits of these routine measurements go beyond identification of short stature. Any child with poor growth needs to be evaluated by a specialist who can go through an extensive differential diagnosis.

Helpful guidelines include the 2009 "Evidence-Based Clinical Practice Guideline on Linear Growth Measurement of Children" from clinicians at Blanks Children's Hospital in Des Moines, Iowa, and "Development of an Evidence-Based Clinical Practice Guideline on Linear Growth Measurement of Children" (J. Pediatr. Nursing 2011;26:312-24).

Sometimes I hear families or primary care physicians say, "Let's just wait and see." It is advisable to see a child back in 6 months to monitor growth velocity, but watching poor linear growth year after year will not optimize the height outcome. The problem with later intervention is that the older child with short stature does not have enough "catch up" time. Therefore, additional evaluation is

warranted if you diagnose short stature and you remain concerned after 6 months.

For a child who warrants this additional evaluation, a bone age x-ray is helpful (although not diagnostic of a specific condition). Other recommended studies include a complete blood count; chemistry panel; free thyroxine (free T4) with thyroid-stimulating hormone

(TSH); insulinlike growth factor 1 (IGF-1), C-reactive protein, urinalysis, and a celiac panel (IgG and IgA class of anti-tissue transglutaminase [anti-tTG]; antientomysial antibodies, IgA class [EMA-IgA]; and quantitative IgA). In addition, for girls, a karyotype can rule out Turner's syndrome.

Obtaining the correct test can sometimes be a problem. For example, IGF-1

is similar to many other test names on a laboratory test list. The odds of a lab technician performing the right test are low, because on their alphabetical test list, IGF BP 1 appears at the top (and this test is not useful at all!). This pitfall can be avoided by including the lab specific test code for IGF-1, which your local pediatric endocrinologist can help you find.

Other testing may be warranted, based

## COMMENTARY

# The Child With Short Stature

*In addition to diet and exercise to improve glycemic*

**ONCE A DAY**  
**kombiglyze XR**  
(saxagliptin and metformin HCl  
extended-release) tablets

**1** **ONE DAILY DOSE** The first and only once-a-day metformin XR + DPP-4 inhibitor\* combination tablet.

Generally taken once-daily with evening meal; gradually titrate dose to reduce GI side effects associated with metformin. Maximum daily recommended dose is 5 mg saxagliptin and 2000 mg metformin XR that can be taken as two 2.5 mg/1000 mg tablets once a day.

\*saxagliptin

### Indication and Important Limitations of Use

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

### Important Safety Information

#### WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

[See Warnings and Precautions]

### Contraindications

- Renal impairment (e.g., serum creatinine levels  $\geq 1.5$  mg/dL for men,  $\geq 1.4$  mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

### Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
  - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR.

Please see adjacent Brief Summary of US Full Prescribing Information including Boxed WARNING about lactic acidosis.

on history and physical findings. For example, if a child has a history of pneumonia and frequent sinusitis, I would order a sweat chloride test to rule out cystic fibrosis.

If there is no clear explanation, and the slowed growth does not respond to your intervention, refer the patient to a specialist.

The growth chart will help guide the type of referral.

If linear growth is poor and weight gain is appropriate (that is, their body mass index is normal), consider referral to a pediatric endocrinologist. If linear

growth is poor, but weight gain is more strikingly affected (that is, BMI is low for age), consider referral instead to a pediatric gastroenterologist. If testing reveals electrolyte abnormalities, consider referral to pediatric nephrology. If the child has congenital anomalies or a developmental delay in addition to short stature, then referral to a ge-

neticist becomes appropriate.

Once a short stature diagnosis is established, a targeted approach geared to the optimization of growth can be planned. Human growth hormone therapy, for example, typically is ordered by a pediatric endocrinologist for a number of diagnoses.

Indications include growth hormone

deficiency, Turner's syndrome, Noonan's syndrome, Prader-Willi syndrome, and children born small for gestational age who fail to catch up. A pediatric nephrologist also might prescribe this therapy for a child with renal failure who is not growing. ■

DR. COUNTS is an associate professor of pediatrics and chief of the division of pediatric endocrinology at the University of Maryland, Baltimore. She works on multiple research studies with funding to the University of Maryland, Baltimore, from Eli Lilly, Pfizer, and Novo Nordisk.

**I hear families or primary care physicians say, 'Let's just wait and see.' The problem ... is that the older child with short stature does not have enough 'catch up' time.**

control in your adult patients with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate



# A dynamic duo

Combining complementary mechanisms  
of action of saxagliptin and metformin XR

- Adverse reactions reported in  $\geq 5\%$  of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%).
- Adverse reactions reported in  $\geq 5\%$  of treatment-naïve patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%).

**Drug Interactions:** Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

#### Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.
- **Pediatric Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

—Metformin: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstated only after renal function is normal.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

#### Adverse Reactions

- Adverse reactions reported in  $>5\%$  of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).

ONCE A DAY  
**kombiglyze XR**  
(saxagliptin and metformin HCl  
extended-release) tablets

[www.kombiglyzxr.com/ad](http://www.kombiglyzxr.com/ad)

 Bristol-Myers Squibb

© 2011 Bristol-Myers Squibb 1144US10AB00817 01/11  
Kombiglyze™ XR is a trademark of Bristol-Myers Squibb

 AstraZeneca

1129602