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An EUA for Sotrovimab for Treatment of COVID-19

Revised 7/1/2021: See page 98.

The investigational monoclonal antibody sotrovimab (VIR-7831; GSK/Vir Biotechnology) has been granted an FDA Emergency Use Authorization (EUA) for treatment of mild to moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease, including hospitalization and death.[1] Sotrovimab is currently under review by Health Canada.[8] Two other monoclonal antibody regimens are authorized for the same indication: casirivimab (REGN10933) and imdevimab (REGN10987) administered together[2] (authorized by interim order for sale in Canada[9]), and bamlanivimab (LY-CoV555) and etesevimab (LYCoV016) administered together[3] (currently under review by Health Canada[10]). The FDA revoked its EUA for bamlanivimab alone in April 2021 because an increasing percentage of COVID-19 cases in the US are being caused by SARS-CoV-2 variants that are resistant to monotherapy with the drug[4]; Health Canada issued a safety alert regarding a potential risk of treatment failure.

Pronunciation Key
Sotrovimab: so troe' vi mab

ELIGIBILITY — The FDA recently expanded the criteria by which a patient with COVID-19 can be considered at high risk for disease progression. All outpatients ≥12 years old who are overweight or pregnant or have cardiovascular disease, hypertension, or chronic respiratory disease are now eligible to receive monoclonal antibody treatment (see Table 1).[5,6]

Use of monoclonal antibodies has been associated with worse clinical outcomes in hospitalized patients with COVID-19 who require high-flow oxygen or mechanical ventilation. Sotrovimab and other mono-clonal antibodies are not authorized for use in patients who are hospitalized for COVID-19 or require oxygen therapy because of COVID-19.

Table 1. High-Risk Conditions for COVID-19 Outpatients[1]

- Age ≥65 years
- BMI ≥25 kg/m^2 (or, in patients 12-17 years old, BMI ≥85th percentile for age and gender[2])
- Pregnancy
- Chronic kidney disease
- Diabetes
- Cardiovascular disease
- Hypertension
- COPD, moderate to severe asthma, or other chronic respiratory disease
- Currently receiving immunosuppressive treatment
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity
- A medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

BMI = body mass index; COPD = chronic obstructive pulmonary disease
1. Adult and pediatric patients (≥12 years old and weighing ≥40 kg) with ≥1 of the criteria listed are considered at high risk for progression to severe COVID-19 and/or hospitalization and are eligible for monoclonal antibody treatment (FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of sotrovimab. Available at: https://www.fda.gov/media/149534/download. Accessed June 3, 2021).
2. Based on CDC growth charts (https://bit.ly/36U0twf).

MECHANISM OF ACTION — Sotrovimab binds to a preserved epitope on the spike protein of SARS-CoV-2. Its exact mechanism of action is unknown, but it appears to prevent membrane fusion after the virus binds to the human ACE2 receptor.

CLINICAL STUDIES — Issuance of the EUA was based on interim results from an unpublished double-blind trial (COMET-ICE; summarized in the FDA Fact Sheet) in 583 adult outpatients with mild to moderate COVID-19 who were ≥55 years old or had at least one comorbidity (diabetes, obesity, chronic kidney disease, heart failure, COPD, or moderate to severe asthma). Patients were randomized to receive a single IV infusion of sotrovimab 500 mg or placebo. The primary endpoint, progression of COVID-19 (hospitalization for >24 hours or death) by day 29, occurred in 1% of patients who received sotrovimab

and in 7% of those who received placebo (HR 0.14 [95% CI 0.04-0.56]; NNT 16.2).[6]

No studies directly comparing sotrovimab with casirivimab and imdevimab or bamlanivimab and etesevimab are available.

VARIANTS — The World Health Organization has renamed COVID-19 variants using the Greek alphabet to avoid confusion and stigmatization. Sotrovimab appears to retain activity against the B.1.1.7 (Alpha; UK), B.1.351 (Beta; South Africa), P.1 (Gamma; Brazil), B.1.427/B.1.429 (Epsilon; California), B.1.526 (Iota; New York), and B.1.617 (Delta; India) variants of SARS-CoV-2. Casirivimab and imdevimab also appear to retain activity against prominent variants, but data on their effectiveness against the B.1.617 strain are lacking. Bamlanivimab and etesevimab are unlikely to have activity against the B.1.351 and P.1 variants; their distribution to states in which these variants cause >10% of COVID-19 cases has been paused.[7]

Treatment-emergent epitope variants were detected in 8 patients who received sotrovimab in COMET-ICE; some of these substitutions conferred reduced susceptibility to the drug.[6]

ADVERSE EFFECTS — The most common adverse effects of sotrovimab in COMET-ICE were rash (2%) and diarrhea (1%). Hypersensitivity reactions, includ-ing anaphylaxis, have occurred rarely with use of monoclonal antibodies, including sotrovimab, for treatment of COVID-19.

DOSAGE AND ADMINISTRATION — Sotrovimab is supplied in 500 mg/8 mL vials, which require refrigeration during storage. The authorized dosage is 500 mg administered as a 30-minute IV infusion after dilution in 50 or 100 mL of normal saline. If the solution cannot be used immediately after dilution, it can be refrigerated for up to 24 hours or left at room temperature for up to 4 hours, including infusion time. Sotrovimab should be allowed to sit at room temperature for 15 minutes before dilution or infusion.

Sotrovimab should be administered as soon as possible after a positive SARS-CoV-2 test result and within 10 days of COVID-19 symptom onset. Patients should be treated in a facility staffed and equipped to manage anaphylaxis; they should be monitored for hypersensitivity reactions during and for at least 1 hour after infusion of the drug.

AVAILABILITY — Sotrovimab is being distributed by the wholesaler AmerisourceBergen while it is available under an EUA. Information on ordering and availability can be found at www.sotrovimab.com/hcp/access.

CONCLUSION — The FDA has issued an Emergency Use Authorization (EUA) for the monoclonal antibody sotrovimab (VIR-7831) for IV treatment of mild to moderate COVID-19 in patients at high risk for progression to severe disease. Sotrovimab is currently under review by Health Canada. In a double-blind trial, use of the drug in high-risk adult outpatients recently diagnosed with COVID-19 decreased the risk of hospitalization or death. Sotrovimab appears to retain efficacy against prominent SARS-CoV-2 variants. No studies directly comparing sotrovimab with other monoclonal antibodies for treatment of COVID-19 are available. ■

1. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes additional monoclonal antibody for treatment of COVID-19. May 26, 2021. Available at: https://bit.ly/2SKgYYf. Accessed June 3, 2021.
2. An EUA for casirivimab and imdevimab for COVID-19. Med Lett Drugs Ther 2020; 62:201.
3. An EUA for bamlanivimab and etesevimab for COVID-19. Med Lett Drugs Ther 2021; 63:49.
4. FDA News Release. Coronavirus (COVID-19) update: FDA revokes Emergency Use Authorization for monoclonal antibody bamlanivimab. April 16, 2021. Available at: https://bit.ly/34Bmjnt. Accessed June 3, 2021.
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Viloxazine ER (*Qelbree*) for ADHD

The FDA has approved viloxazine extended-release capsules (*Qelbree* – Supernus; not approved in Canada) for treatment of attention-deficit/hyperactivity disorder (ADHD) in children 6-17 years old. Viloxazine is the second selective norepinephrine reuptake inhibitor to be approved in the US for treatment of ADHD; atomoxetine (*Strattera*, and generics) was approved in 2002 in the US and in 2005 in Canada.

Pronunciation Key	
Viloxazine: vye lox' a zeen	***Qelbree*:** kel' bree

STANDARD TREATMENT — Stimulants such as amphetamines and methylphenidate are the drugs of choice for treatment of ADHD. They are classified as Schedule II controlled substances (in Canada, they are classified as Schedule III controlled substances).

Common adverse effects include decreased appetite, weight loss, abdominal pain, headache, and delayed sleep onset. Long-term stimulant use has been associated with suppression of adult height. Psychotic symptoms and cardiovascular events can occur.

Nonstimulants such as atomoxetine and the alpha$_2$-agonists clonidine and guanfacine are not controlled substances. They are less effective than stimulants but may be preferred for school-age children because they cause fewer adverse effects.[1] Nonstimulants can be used as initial monotherapy, in combination with stimulants, or when stimulants are contraindicated, ineffective, or not tolerated. Atomoxetine can cause somnolence, nausea, vomiting, increases in heart rate and blood pressure, and growth delays, and has been associated with an increased risk of suicidal thoughts. Clonidine and guanfacine can cause somnolence, dizziness, and hypotension.

Parent Training in Behavior Management (PTBM) and/or behavioral classroom interventions are strongly recommended as an adjunct to pharmacotherapy in school-age patients.[2]

MECHANISM OF ACTION — Like atomoxetine, viloxazine inhibits reuptake of norepinephrine in the brain. It is a less potent norepinephrine reuptake inhibitor than atomoxetine; the clinical significance of this difference is unknown. Unlike atomoxetine, viloxazine also acts *in vitro* as a serotonin (5-HT)$_{2B}$ agonist and a 5-HT$_{2C}$ antagonist. In animal studies, viloxazine has increased extracellular 5-HT levels in the prefrontal cortex, and its effects on 5-HT receptors have been shown to suppress hyperlocomotion.[3]

Table 1. Pharmacology

Class	Selective norepinephrine reuptake inhibitor
Formulation	100, 150, 200 mg extended-release capsules
Route	Oral
Tmax (median)	~5 hours; a high-fat meal delays Tmax by ~2 hours
Metabolism	Primarily by CYP2D6, UGT1A9, and UGT2B15
Elimination	Renal (90% in urine, <1% in feces)
Half-life (mean)	7.02 hours

CLINICAL STUDIES — FDA approval of viloxazine ER for treatment of ADHD was based on the results of three randomized, double-blind, placebo-controlled trials, two in children 6-11 years old and the third in adolescents 12-17 years old. After a dose titration phase, patients received once-daily maintenance treatment with viloxazine or placebo for 5 weeks. In all three trials, mean improvement from baseline in ADHD symptoms, evaluated using the ADHD Rating Scale (ADHD-RS-5; the primary endpoint) and the Clinical Global Impression-Improvement (CGI-I) scale, was significantly greater with the active drug than with placebo (see Table 2).[4-6]

Table 2. Viloxazine Clinical Trial Results

Regimen	ADHD-RS-5 Score[1] Baseline	Change	CGI-I Score[2]
Trial 1 (6-11 years old; 6 weeks[3]; n=477)[4]			
Viloxazine ER 200 mg/day	44.0	-17.7*	2.6*
Viloxazine ER 100 mg/day	45.0	-16.6*	2.7*
Placebo	43.6	-10.9	3.1
Trial 2 (6-11 years old; 8 weeks[3]; n=313)[5]			
Viloxazine ER 400 mg/day	45.0	-17.5*	2.4*
Viloxazine ER 200 mg/day	43.8	-17.6*	2.5*
Placebo	43.5	-11.7	3.0
Trial 3 (12-17 years old; 6 weeks[3]; n=310)[6]			
Viloxazine ER 400 mg/day	39.4	-16.5*	2.6*
Viloxazine ER 200 mg/day	39.9	-16.0*	2.6*
Placebo	40.5	-11.4	3.1

*Statistically significant difference vs placebo; ER = extended-release

1. ADHD Rating Scale-5. Mean scores rated on a scale of 0-56, with higher scores indicating more severe ADHD symptoms.
2. Clinical Global Impression-Improvement score. Mean scores rated on a scale of 1-7, with 1 indicating much improved ADHD symptoms and 7 indicating much worse ADHD symptoms compared to baseline. Data available in the FDA Integrated Review: https://www.fda.gov/media/148484/download. Accessed June 10, 2021.
3. Each trial consisted of a 1- or 3-week dose titration phase and a 5-week maintenance phase.
4. A Nasser et al. Clin Ther 2020; 42:1452.
5. A Nasser et al. Clin Ther 2021 March 6 (epub).
6. A Nasser et al. J Clin Psychopharmacol 2021 May 5 (epub).

ADVERSE EFFECTS — In clinical trials, somnolence, fatigue, insomnia, decreased appetite, irritability, nausea, vomiting, and headache occurred in ≥5% of patients who took viloxazine and more often with the active drug than with placebo. Weight loss and failure to gain weight have been reported. Patients starting viloxazine should be counseled to avoid activities requiring mental alertness until they know how the drug will affect them.

Increases in heart rate (≥20 bpm at any time point) and diastolic blood pressure (≥15 mm Hg at any time point) occurred more often with viloxazine than with placebo in clinical trials. Heart rate and blood pressure should be monitored after dosage increases and periodically during treatment.

As with atomoxetine, the package insert for viloxazine contains a boxed warning about a risk of suicidal thoughts and behavior with use of the drug. In clinical trials, suicidal ideation or behavior was reported in 0.9% (9/1019) of patients taking viloxazine and in 0.4% (2/463) of those taking placebo.

Noradrenergic drugs may increase the risk of a manic or mixed episode in patients with bipolar disorder. Patients should be screened for their risk of developing bipolar disorder before starting viloxazine.

PREGNANCY AND LACTATION — Viloxazine was associated with fetal and maternal toxicity in animal

Table 3. Selective Norepinephrine Reuptake Inhibitors for ADHD

Drug	Pediatric Dosage Initial/Maximum[1]	US Cost[2]	CAN Cost[5]
Atomoxetine – generic *Strattera* (Lilly)	0.5 mg/kg/day in a single dose or divided bid/ 1.4 mg/kg/day in a single dose or divided bid (max 100 mg/day)[3]	$101.80[4] 395.40[4]	$19.30[4] 121.80[4]
Viloxazine ER – *Qelbree* (Supernus)	**6-11 yrs:** 100 mg once daily/ 400 mg once daily **12-17 yrs:** 200 mg once daily/ 400 mg once daily	299.00	N.A.C.

ER = extended-release; N.A.C. = not available in Canada

1. For children ≥6 years old. Dosage adjustments for renal or hepatic impairment or for drug or genome interactions may be required.
2. Approximate WAC for 30 days' treatment at the initial dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.
3. Dosage for children weighing ≤70 kg. Children weighing >70 kg should take the adult dosage (40 mg once daily/100 mg once daily or divided bid).
4. Cost of 25-mg capsules.
5. Approximate WAC for 30 days' treatment at the initial dosage, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, June 2021).

studies; the drug should not be used during pregnancy. No data are available on the presence of viloxazine in breast milk or its effects on the breastfed infant or milk production.

DRUG INTERACTIONS — Use of viloxazine with a monoamine oxidase inhibitor (MAOI) or within 2 weeks after stopping an MAOI can increase the risk of hypertensive crisis and is contraindicated.

Viloxazine is a strong CYP1A2 inhibitor; in pharmacokinetic studies, exposure to caffeine, a CYP1A2 substrate, increased 6-fold with coadministration of viloxazine. Patients taking viloxazine should be advised to limit the use of or avoid products containing caffeine. Use of viloxazine with CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline) is contraindicated. Viloxazine is also a weak inhibitor of CYP2D6 and 3A4; it may increase exposure to substrates of these isozymes.[7]

In an open-label crossover study in 34 healthy adults, coadministration of viloxazine and methylphenidate did not affect the pharmacokinetics of either drug.[8]

DOSAGE AND ADMINISTRATION — The recommended starting dosage of viloxazine is 100 mg once daily in children 6-11 years old and 200 mg once daily in adolescents 12-17 years old. The daily dose can be titrated weekly in increments of 100 mg (age 6-11 years) or 200 mg (age 12-17 years) to a maximum of 400 mg (see Table 3).

Key Points: Viloxazine ER (*Qelbree*)

- An extended-release selective norepinephrine reuptake inhibitor FDA-approved for once-daily treatment of ADHD in children 6-17 years old.
- Not approved in Canada.
- Improved ADHD symptoms significantly more than placebo in three short-term double-blind clinical trials.
- Somnolence, increases in heart rate and blood pressure, weight loss or failure to gain weight, and suicidal ideation may occur.
- Viloxazine is a strong CYP1A2 inhibitor; use with CYP1A2 substrates with a narrow therapeutic index is contraindicated.

In patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), the recommended starting dosage of viloxazine is 100 mg once daily. The daily dose can be titrated weekly in increments of 50 or 100 mg to a maximum of 200 mg.

Viloxazine capsules can be swallowed whole or their contents can be sprinkled over a teaspoonful of applesauce and consumed within 2 hours.

CONCLUSION — In short-term clinical trials, the selective norepinephrine reuptake inhibitor viloxazine (*Qelbree*; not approved in Canada) was more effective than placebo for treatment of ADHD in children 6-17 years old. As with atomoxetine (*Strattera*, and generics), the other selective norepinephrine reuptake inhibitor approved for treatment of ADHD, somnolence, increases in heart rate and blood pressure, weight loss or failure to gain weight, and suicidal ideation may occur with its use. How viloxazine compares in efficacy with atomoxetine or other nonstimulants for treatment of ADHD is unknown. Stimulants are preferred for most patients. ■

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2. Drugs for ADHD. Med Lett Drugs Ther 2020; 62:9.
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Estetrol/Drospirenone (*Nextstellis*) – A New Combination Oral Contraceptive

Health Canada and the FDA have approved a combination oral contraceptive containing the estrogen estetrol and the progestin drospirenone (*Nextstellis* – Searchlight Pharma; Mithra/Mayne in the US). Estetrol is the first new estrogen to become available in Canada and the US in 50 years. Drospirenone is available alone (*Slynd*; not approved as a single entity in Canada) and in combinations with the estrogen ethinyl estradiol for prevention of pregnancy.[1]

Pronunciation Key

Estetrol: es' te trol **Nextstellis:** next' ste lis"

CHOICE OF CONTRACEPTIVES — Intrauterine devices (IUDs) and the etonogestrel implant (*Nexplanon*) have typical-use first-year failure rates of <1%, but they require an office visit for placement and removal. Combination and progestin-only oral contraceptives, transdermal patches, vaginal rings, and injectable medroxyprogesterone acetate have typical-use first-year failure rates of 6-7%. Barrier and behavioral-based methods are less effective.[2]

ESTETROL/DROSPIRENONE — Estetrol is a synthetic version of a native estrogen produced in the human fetal liver.[3] It has a longer half-life than micronized estradiol (24-32 hours vs 10-12 hours); the longer half-life theoretically could decrease rates of unscheduled bleeding. Unlike other estrogens, estetrol is highly selective for nuclear estrogen receptors alpha and beta and acts as an antagonist at the membrane estrogen receptor. These properties theoretically could reduce the risk of estrogen-related adverse effects, including venous thromboembolism (VTE).[4] A small study comparing 5- and 10-mg doses of estetrol (lower than the marketed dose) with ethinyl estradiol 20 mcg, both combined with drospirenone 3 mg, found that the new hormone had less effect on markers of hemostasis.[5]

Drospirenone has antiandrogenic properties that may improve acne, but it also has antimineralocorticoid activity that can cause hyperkalemia if it is used with other drugs that increase serum potassium levels.

MECHANISM OF ACTION — Like other combination oral contraceptives, estetrol/drospirenone prevents pregnancy primarily by suppressing ovulation, but it also thickens cervical mucus.

CLINICAL STUDIES — Approval of *Nextstellis* was based on the results of two single-arm trials (one in the US/Canada and one in Europe/Russia); only the US/Canada trial has been published.[6] Women in both trials received active tablets containing estetrol 15 mg/drospirenone 3 mg once daily for 24 days, followed by 4 inactive tablets once daily for up to 13 cycles.

Key Points: Estetrol/Drospirenone (*Nextstellis*)

- A combination oral contraceptive containing the new estrogen estetrol and the progestin drospirenone.
- Taken daily with a 4-day hormone-free interval at the end of the cycle (24 active tablets and 4 inactive tablets).
- Effective in preventing pregnancy in two clinical trials.
- Theoretical advantages in safety over other combination oral contraceptives require validation in large comparative trials.

The US/Canada trial (E4 FREEDOM) included 1524 women 16-35 years old with a body mass index (BMI) ≤35 kg/m^2 who completed a total of 12,763 evaluable 28-day cycles. The Pearl Index (pregnancy rate per 100 woman-years of use), the primary endpoint, was 2.65 in women 16-35 years old, 2.57 in women with a BMI <30 kg/m^2, and 2.94 in those with a BMI 30-<35 kg/m^2. These rates are similar to those with other recently approved oral contraceptives.[6]

The Europe/Russia trial (also called E4 FREEDOM) included 1353 women 16-35 years old with a BMI ≤35 kg/m^2 who completed a total of 13,692 evaluable 28-day cycles. The Pearl Index was 0.47, according to the manufacturer.

In another open-label trial in 82 women, estetrol 15 mg/drospirenone 3 mg for 3 consecutive cycles was similar in efficacy to ethinyl estradiol 20 mcg/drospirenone 3 mg in suppressing ovulation.[7]

ADVERSE EFFECTS — The most common adverse effects of *Nextstellis*, occurring in ≥2% of women in the E4 Freedom trials, were bleeding irregularities, mood disturbance, headache, breast symptoms, dysmenorrhea, acne, weight gain, and decreased libido. Use of estetrol/drospirenone

Table 1. Contraindications to *Nextstellis* Use

- Pregnancy
- High risk of arterial or venous thrombotic events[1]
- Current or history of breast cancer or other estrogen- or progestin-sensitive cancer
- Liver disease (tumor, acute viral hepatitis, or decompensated cirrhosis)
- Undiagnosed abnormal uterine bleeding
- Concurrent administration of hepatitis C drugs containing ombitasvir/paritaprevir/ritonavir
- Renal impairment
- Adrenal insufficiency

1. Includes women who are >35 years old and smoke, have current or a history of deep vein thrombosis or pulmonary embolism, or have cerebrovascular disease, coronary artery disease, thrombogenic valvular or thrombogenic rhythm disease, inherited or acquired hypercoagulopathies, uncontrolled hypertension or hypertension with vascular disease, migraine headaches with aura, diabetes with hypertension or vascular disease or other end-organ damage, or diabetes of >20 years' duration.

Table 2. Timing of *Nextstellis* Dose

Patient Population	*Nextstellis* Dose
Women not currently using a hormonal contraceptive	During the first 24 hours of menstruation; if not taken within first 24 hours, backup contraception recommended for 7 days
Women switching from a hormonal combination oral contraceptive, transdermal patch, or vaginal ring	On the first day of the next treatment cycle or the next scheduled dose of the oral contraceptive
Women switching from an implant or a hormonal IUD	On the day the implant or IUD has been removed
Women switching from a progestin-only contraceptive	On the first day of the next treatment cycle
Women who had a first-trimester abortion or miscarriage	Within first 7 days after termination; backup contraception required for next 7 days
Women who had a second-trimester abortion or miscarriage (>14 weeks but ≤20 weeks' gestation)	At least 4 weeks after termination; backup contraception recommended for first 7 days
Postpartum women not breastfeeding	At least 4 weeks after childbirth; backup contraception recommended for first 7 days

was associated with one VTE in the Europe/Russia trial and no VTEs in the US/Canada trial.[8] There is no acceptable evidence that estetrol/drospirenone is less likely than other combination oral contraceptives to cause these adverse effects.

DRUG INTERACTIONS — Unlike ethinyl estradiol, estetrol is not metabolized by CYP isozymes. Drospirenone is a CYP3A4 substrate. CYP3A4 inducers, such as rifampin, can increase the metabolism of drospirenone and decrease its effectiveness. CYP3A4 inhibitors taken concurrently with drospirenone could increase the risk of hyperkalemia and other adverse effects.[9]

Concurrent use of drospirenone with other drugs that increase potassium levels, such as spironolactone (*Aldactone*, and generics), which is often used off-label for treatment of acne, can increase the risk of hyperkalemia. Concomitant use of a bile acid seques-trant with *Nextstellis* may decrease estetrol and drospirenone concentrations and their effectiveness. *Nextstellis* may increase serum concentrations of some systemic corticosteroids, and it can increase thyroid-binding globulin concentrations in patients also taking thyroid hormone replacement therapy; more frequent monitoring of corticosteroid adverse effects or of thyroid-stimulating hormone levels may be needed.

DOSAGE, ADMINISTRATION, AND COST — *Nextstellis* is available in blister cards containing 24 active (estetrol 14.2 mg/drospirenone 3 mg) and 4 inactive tablets. Women not currently using a hormonal contraceptive should take the first active tablet on the first day of menses; subsequent tablets (including inactive tablets) should be taken once daily at the same time each day. If an active tablet dose is missed, it should be taken as soon as possible and the next tablet should be taken at the scheduled time. If vomiting or diarrhea occurs within 3-4 hours after taking estetrol/drospirenone, a new tablet should be taken as soon as possible. The label includes detailed instructions for subsequent doses if ≥2 active tablet doses are missed.

The cost of 28 days' treatment with *Nextstellis* is US$190 (price not yet available in Canada), compared to US$8-12 (CAN$9-12) for generic combination oral contraceptives containing ethinyl estradiol and drospirenone.[10]

CONCLUSION — The combination oral contraceptive *Nextstellis,* which contains the new estrogen estetrol and the progestin drospirenone, appears to be as effective in preventing pregnancy as other recently approved oral contraceptives, but there is no acceptable evidence that it is safer. Until data from large comparative trials become available, generic combination oral contraceptives available at a fraction of the cost are preferred. ■

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10. Approximate WAC. WAC=wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.

Jatenzo – An Oral Testosterone for Hypogonadism

An oral formulation of testosterone undecanoate (*Jatenzo* – Clarus; not approved in Canada) has been approved by the FDA for treatment of adult men with conditions associated with a deficiency of endogenous testosterone, such as Klinefelter syndrome, orchiectomy, toxic damage from chemotherapy or alcohol, or pituitary-hypothalamic injury from tumors, trauma, or radiation; testosterone undecanoate has been available as an oral preparation in Canada since 1992. *Jatenzo* is not approved for treatment of low testosterone levels solely due to aging. It is the first oral testosterone formulation to be approved in the US.

Pronunciation Key
Jatenzo: juh ten' zoh

HYPOGONADISM – Inadequate testicular production of testosterone can lead to loss of energy, irritability, depression, decreased libido, erectile dysfunction, decreased axillary and pubic hair, loss of muscle mass, anemia, and osteoporosis. The normal physiologic range for serum testosterone concentrations (usually 300-1000 ng/dL) is based on levels found in young men.

TESTOSTERONE REPLACEMENT – Oral testosterone replacement therapy has generally been ineffective because of gut-wall and first-pass metabolism. Earlier oral formulations (17α-alkylated testosterone

Table 1. Some Testosterone Replacement Products[1]

Drug	Some Formulations	Usual Adult Dosage[2]	US Cost[3]	CAN Cost[12]
Injectable				
Testosterone cypionate – generic	1, 10 mL vials (100, 200 mg/mL)[4,5,13]	50-400 mg IM q2-4 weeks	$74.90	$39.50
Depo-Testosterone (Pfizer)			77.20	50.80
Testosterone enanthate – generic	5 mL vials (200 mg/mL)[5]	100-200 mg IM q2 weeks	74.70	N.A.C.
Xyosted (Antares Pharma)	0.5 mL auto-injectors (50, 75, 100 mg/0.5 mL)	50-100 mg SC once/week	523.70	N.A.C.
Delatestryl (Valeant)	5 mL vial (200 mg/mL)	100-400 mg IM q4 weeks	N.A.	59.70
Testosterone undecanoate – *Aveed* (Endo)[6]	3 mL vials (250 mg/mL)	750 mg IM at 0 and 4 weeks, then q10 weeks	1416.80	N.A.C.
Implant				
Testosterone – *Testopel* (Endo)	75 mg pellets	150-450 mg SC q3-6 months[7]	216.40	N.A.C.
Transdermal				
Testosterone 1% gel – generic	25 mg/2.5 g, 50 mg/5 g packets; 50 mg/5 g tubes; 75 g, 88 g MDP (12.5 mg/1.25 g actuation)[14]	50 mg once/day	313.10	88.70
AndroGel 1% (BGP Pharma; Abbvie in US)	25 mg/2.5 g, 50 mg/5 g packets[15]		640.50	134.20
Testim (Paladin; Endo in US)	50 mg/5 g tube		592.10	127.50
Testosterone 1.62% gel – generic	20.25 mg/1.25 g, 40.5 mg/2.5 g packets; 75 g MDP (20.25 mg/1.25 g actuation)	40.5 mg once/day	552.60	N.A.C.
AndroGel 1.62% (Abbvie)			640.50	N.A.C.
Testosterone 2% gel – generic	60 g MDP (10 mg/0.5 g actuation)	40 mg once/day[8]	349.60	N.A.C.
Fortesta (Endo)			414.20	N.A.C.
Testosterone patch – *Androderm* (Allergan; Abbvie in US)	2, 4 mg/day patch[16]	4 mg once/night[17]	615.90	145.80[18]
Testosterone solution – generic[9]	90 mL MDP (30 mg/1.5 mL actuation)	60 mg once/day[10]	405.50	N.A.C.
Intranasal				
Testosterone gel – *Natesto* (Acerus)	11 g MDP (5.5 mg/0.122 g actuation)	11 mg tid[11]	577.60	N.A.C.
Oral				
Testosterone undecanoate – *Jatenzo* (Clarus)	158, 198, 237 mg caps	158-396 mg bid	458.80	N.A.C.
generic	40 mg caps	40-120 mg once/day	N.A.	14.10

MDP = metered-dose pump; N.A.C. = not available in Canada; N.A. = not available in the US
1. All testosterone products are classified as Schedule III controlled substances.
2. Dosage and titration is based on total serum testosterone concentrations.
3. Approximate wholesale acquisition cost (WAC) for one 10-mL vial (100 mg/mL) of testosterone cypionate, one 5-mL vial of testosterone enanthate, four *Xyosted* auto-injectors, one 3-mL vial of *Aveed*, 2 pellets of *Testopel*, or a 30-day supply at the lowest usual adult dosage. When multiple dosage forms are available, the cost of the packet is given. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.
4. The 100-mg/mL formulation is only available in a 10-mL vial.
5. Vial should be discarded within 28 days after being opened or accessed (USP General Chapter 797).
6. Only available to certified prescribers through a REMS program because of the risk of serious pulmonary oil microembolism reactions and anaphylaxis.
7. Implant 2 pellets for each 25 mg of testosterone propionate required weekly.
8. Administered as 2 pump actuations to each thigh.
9. For axillary application. *Axiron*, the reference product for this formulation, is no longer marketed.
10. Administered as 1 pump actuation (30 mg) to each axilla.
11. Administered as 1 pump actuation (5.5 mg) in each nostril.
12. Approximate WAC for one 10-mL vial (100 mg/mL) of testosterone cypionate, one 5-mL vial of testosterone enanthate, or a 30-day supply at the lowest usual dosage, based on prices in Canadian dollars from a national wholesaler (prices in Ontario, June 2021).
13. Only 100 mg/mL (10 mL) vials available in Canada.
14. In Canada, available as 25 mg/2.5 g gel and 50 mg/5 g gel packet.
15. In Canada, also available as pump (12.5 mg/1.25 g actuation).
16. In Canada, available as 2.5 mg/day and 5 mg/day patch.
17. In Canada, 5 mg once/night.
18. Cost for 5 mg patch.

derivatives), which are still available in Europe but not in Canada or the US, have been associated with hepatotoxicity and hepatic adenocarcinoma. Injectable, transdermal, and intranasal formulations can raise serum testosterone concentrations into the normal range, but injection-site pain, transference of the drug to women and children, and skin and nasal irritation have been reported with some of these formulations.[1] Testosterone cypionate, undecanoate (not available in Canada as an injection), and enanthate are available in long-acting intramuscular formulations. Fluctuations in serum testosterone concentrations that occur with IM injection every 2-4 weeks may result in adverse effects early in the dosing interval and loss of efficacy at the end of the dosing interval. All testosterone products are classified by the DEA as Schedule III controlled substances.

THE NEW FORMULATION — *Jatenzo* contains testosterone undecanoate, a prodrug formed by attaching a fatty acid to testosterone. The lipophilic prodrug combines with lipoprotein particles in the intestine and is absorbed into the intestinal lymphatic system, bypassing hepatic metabolism.

CLINICAL STUDIES — FDA approval of oral testosterone undecanoate was based on the results of an open-label trial (inTUne) in 222 hypogonadal men who were randomized to receive oral testosterone undecanoate twice daily or topical testosterone 2% once daily for 3-4 months. The proportion of patients who had a mean plasma total testosterone concentration within the eugonadal range at the final visit, the primary endpoint, was 87% in both groups.[2]

In another trial in 86 hypogonadal men, serum testosterone concentrations remained in the normal range after 2 years of treatment with oral testosterone undecanoate, and no hepatotoxicity was observed.[3]

ADVERSE EFFECTS — *Jatenzo* can cause polycythemia, venous thromboembolism, azoospermia, peripheral edema, gynecomastia, sleep apnea, decreases in HDL levels, hypercalcemia, increases in hematocrit, depression, and suicidal ideation and behavior.

Increases in blood pressure can occur with *Jatenzo*; patients taking the drug should be monitored for new-onset hypertension and exacerbations of preexisting hypertension. Whether testosterone replacement therapy increases the risk of major adverse cardiovascular events is unclear. Testosterone replacement therapy has been associated with increases in prostate-specific antigen (PSA) concentrations, but whether it increases the risk of prostate cancer is also unclear.[4]

DOSAGE AND ADMINISTRATION — The recommended starting dosage of *Jatenzo* is 237 mg orally twice daily with food. The dose should be adjusted (mini-mum of 158 mg and maximum of 396 mg) based on serum testosterone concentrations measured 6 hours after the morning dose at least 7 days after starting treatment or following dosage adjustments.

CONCLUSION — Oral testosterone undecanoate (*Jatenzo;* not approved in Canada) appears to be an effective and convenient option for testosterone replacement in hypogonadal men; in Canada, oral testosterone undecanoate is available as an oral capsule (generic). *Jatenzo* is not approved for treatment of low testosterone levels solely due to aging. ■

Key Points: Testosterone Undecanoate (*Jatenzo*)

- FDA-approved for treatment of adult men with conditions associated with a deficiency of endogenous testosterone. It is not approved for treatment of low testosterone levels solely due to aging.
- Not approved in Canada.
- First oral formulation of testosterone to be approved in the US.
- Testosterone undecanoate has been available as an oral capsule in Canada since 1992.
- In two clinical trials, 87% of hypogonadal men taking oral testosterone undecanoate achieved serum testosterone concentrations within the eugonadal range.
- As with other testosterone replacement products, increases in blood pressure and PSA concentrations can occur.

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The expected outcome of the CME program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *The Medical Letter*. The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare providers through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter does not sell advertising or receive any commercial support.

GOAL:

Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

DISCLOSURE:

Principal Faculty for this Activity:
Mark Abramowicz, M.D., President: no disclosure or potential conflict of interest to report.
Jean-Marie Pflomm, Pharm.D., Editor in Chief: no disclosure or potential conflict of interest to report.
Brinda M. Shah, Pharm.D., Consulting Editor: no disclosure or potential conflict of interest to report.

In addition to the Principal Faculty above, the following have also contributed to this activity:
Michael P. Viscusi, Pharm.D., Associate Editor: no disclosure or potential conflict of interest to report.
Cynthia Covey has disclosed that her spouse is employed by a company that has pharmaceutical companies as clients and his work relates to the development of marketing materials for companies such as Merck and BMS.

LEARNING OBJECTIVES FOR THIS ACTIVITY:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in *The Medical Letter* with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:
1. Review the efficacy and safety of sotrovimab for treatment of COVID-19.
2. Review the efficacy and safety of viloxazine extended-release capsules *(Qelbree)* for treatment of ADHD.
3. Review the efficacy and safety of estetrol/drospirenone *(Nextstellis)* for prevention of pregnancy.
4. Review the efficacy and safety of oral testosterone undecanoate *(Jatenzo)* for treatment of hypogonadism.

CREDIT:

Participants who complete this activity and achieve a score of 70% or higher on the post-activity exam will be awarded 2 credits.

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Note: The participant should read the post-activity questions prior to beginning the activity. After careful review of the text, tables, and cited references, the participant should take time to reflect on how the newly acquired knowledge will be applied to clinical practice, affect patient care, and improve outcomes.

Issue 1627 Post-Activity Questions

(Correspond to questions #121-130 in Comprehensive Activity #84, available July 2021)

An EUA for Sotrovimab for Treatment of COVID-19

1. Sotrovimab:
   a. was more effective than the combination of casirivimab and imdevimab in decreasing the risk of hospitalization or death in high-risk adult outpatients recently diagnosed with COVID-19
   b. appears to retain efficacy against prominent SARS-CoV-2 variants, including B.1.1.7 (Alpha; UK) and B.1.617 (Delta; India)
   c. is authorized for use in patients who require oxygen therapy because of COVID-19
   d. all of the above
2. Which of the following outpatients with mild to moderate COVID-19 is considered to be at high risk for progression to severe disease?
   a. a 19-year-old woman with type 1 diabetes and a BMI of 24 kg/m^2
   b. a 40-year-old man with chronic kidney disease and a BMI of 26 kg/m^2
   c. a 34-year-old otherwise healthy woman with a BMI of 28 kg/m^2
   d. all of the above

Viloxazine ER *(Qelbree)* for ADHD

3. Viloxazine has been shown to be effective for treatment of ADHD in:
   a. preschool-age children
   b. children 6-17 years old
   c. adults
   d. all of the above
4. Extended-release viloxazine can cause:
   a. increases in heart rate
   b. increases in blood pressure
   c. decreased appetite
   d. all of the above

Estetrol/Drospirenone *(Nextstellis)* – A New Combination Oral Contraceptive

5. Which of the following contraceptive methods has a typical-use first-year failure rate of <1%?
   a. condoms
   b. progestin-only oral contraceptives
   c. intrauterine devices
   d. injectable medroxyprogesterone acetate
6. Compared to ethinyl estradiol, estetrol:
   a. has a longer half-life
   b. has been shown in a randomized trial to be more effective in preventing pregnancy
   c. has been shown in a randomized trial to be less likely to cause venous thromboembolism
   d. all of the above
7. Which of the following adverse effects occurred in ≥2% of women who took *Nextstellis* in the pivotal clinical trials?
   a. acne
   b. weight gain
   c. bleeding irregularities
   d. all of the above

***Jatenzo* – An Oral Testosterone for Hypogonadism**

8. In the inTUne clinical trial, the proportion of patients treated with oral testosterone undecanoate who had mean total testosterone serum concentrations within the eugonadal range at the final visit was:
   a. the same as that with testosterone undecanoate given IM once weekly
   b. lower than that with intranasal testosterone given three times daily
   c. the same as that with topical testosterone 2% applied once daily
   d. higher than that with placebo
9. Adverse effects of testosterone replacement therapy include:
   a. increased prostate-specific antigen concentrations
   b. gynecomastia
   c. venous thromboembolism
   d. all of the above
10. Which of the following statements about oral testosterone undecanoate is true?
    a. patients treated with the drug should be monitored for hypertension
    b. the dosage should be adjusted based on serum testosterone concentrations measured 6 hours after the morning dose at least 7 days after starting treatment
    c. it is classified as a Schedule III controlled substance
    d. all of the above

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