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Paxlovid™ (nirmatrelvir/ritonavir) Now Available Directly from Pharmacist

Dr. Kim Broedel-Zaugg, R .Ph., M.B.A., Ph.D.

In early July, the Food and Drug Administration started permitting pharmacists to screen patients for COVID-19 and prescribe Paxlovid just as hospitalizations and deaths began to rise from the virus. Timing is extremely important as the drug must be started within five days of being symptomatic. This authorization should increase access to the medication. However, patients will need to supply important information to the pharmacist prior to receiving Paxlovid.[1]

Patients must:

- Present recent health records including blood tests completed in the last 12 months
- Provide current list of prescription and over the counter medications
- Test positive for COVID-19 and be symptomatic

Pharmacists must:

- Review laboratory values for possible liver or kidney problems
- Review medication lists for possible contraindications or medication interactions
- Refer patient to medical practitioner if information is not adequate, liver/kidney function inadequate, medication therapy requires modification[2,3]

If the patient's local pharmacy does not provide this service, patients may also seek out a Test-to Treat site.[2]

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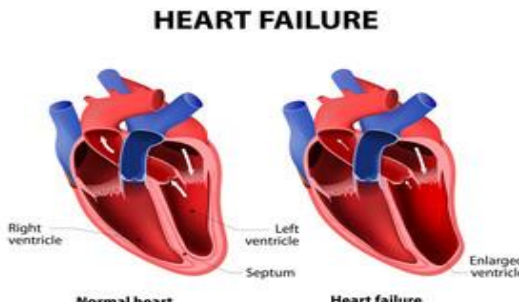
2. Coronavirus (COVID-19) Update: FDA Authorizes Pharmacists to Prescribe Paxlovid with Certain Limitations | FDA. Accessed 7-18-22.
3. Test to Treat for Paxlovid (pharmacist.com). Accessed 7-18-22.



New Novel Agent for the Management of Heart Failure

Kenneth Canipe, PharmD, BCCCP

On January 19th, 2021, the FDA approved a new novel agent for the management of heart failure.[2,3] Vericiguat (Verquvo®) works to enhance the production of cyclic guanosine monophosphate (cGMP) by directly stimulating soluble guanylate cyclase independent of nitric oxide. It also works to enhance soluble guanylate cyclase sensitivity to endogenous nitric oxide, resulting in increased levels of cGMP production.[3] This increase in levels of cGMP lead to smooth muscle relaxation and vasodilation therefore decreasing afterload. Vericiguat was approved based on the results of the VICTORIA study, which showed a lower incidence of death from cardiovascular causes and hospitalization from heart failure versus placebo.[1] The VICTORIA study included 5050 patients with chronic heart failure (New York Heart Associate class II, III, or IV) with an ejection fraction of less than 45%. Patients were started on a dose of 2.5 mg daily and then titrated as tolerated to a target dose of 10 mg daily (titrations were every 2 weeks as tolerated).[1]

One important boxed warning associated with vericiguat is that pregnancy should be excluded before initiation of the medication.[2] Also female patients should be counseled to use effective forms of contraception during treatment and up to one month after treatment.[2,3] Other notable exclusion criteria included a systolic blood pressure of less than 100 mmHg, IV inotrope use or current/anticipated placement of an implantable LVAD, a stroke or TIA within 60 days of starting, GFR less than 15 mL/min, chronic dialysis, or continuous home oxygen use for severe pulmonary disease.[1] The study did have some weakness in that only 60% of patients were on heart failure triple therapy, the type of beta blocker was not specifically looked at, the use of SGLT2 inhibitors was only seen in a small number of patients and the study had a short term of follow up at ~ 10.8 months.[1]

Even though vericiguat was approved in January 2021, it was not added to guidelines until May 2022. The 2022 AHA/ACC/HFSA guidelines recommendation for vericiguat is as follows: "In select high-risk patients with HFrEF and recent worsening of heart failure already on guideline-directed medical therapy (GDMT), an oral soluble cyclase simulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death".[4] This recommendation was given a 2b class of recommendation (weak: benefit>risk) with a B-R level of evidence (Moderate-quality evidence).[4] Given the weak recommendation, potential costs of this new medication, and the potential decrease in compliance with an already complicated medication regimen (due to pill burden), vericiguat will probably not be seen in very many patients with heart failure. Pending new evidence, the use of guideline-directed medical therapy should the main focus for patients living with heart failure.

References:

1. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. NEJM. 2020; 382(20): 1883-1893.
2. Verquvo [Package Insert]. Rahway, NJ: Merck Sharp & Dohme LLC; 2021.
3. Vericiguat. In: Lexi-Drugs Online [database on Android® Device]. Hudson (OH): Lexi-Comp, Inc.; 2021 [Cited 18 July 2022]. Available from: http://online.lexi.com. Subscription required to view.
4. Heidenreich P, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary. *J Am Coll Cardiol.* 2022 May, 79 (17) 1757–1780.**https://doi.org/10.1016/j.jacc.2021.12.011**

Inclisiran

Robert Stanton, M.B.A., Pharm.D., BCPS

Inclisiran (Leqvio)

The FDA has approved inclisiran subcutaneous injection as a treatment for heterozygous familial hypercholesteremia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) in adult patients who are on maximally tolerated statin therapy who need additional LDL-C lowering.

Initial clinical results were good with an average 50% reduction in patients on maximally tolerated statins and inclisiran.

Mechanism of Action

Inclisiran works indirectly through the PCSK9 proprotein. It is a small interfering RNA (siRNA) which affects PCSK9. Inclisiran is considered an oligonucleotide. As an oligonucleotide, inclisiran can elicit an immune response including potentially neutralizing antibodies. In the 18-month clinical trial there was no indication anti-drug antibodies affected clinical response, but the long-term effect of anti-drug antibodies is unknown.

Dosage

Patients receive two initial doses, the initial dose and 1 more three months later, and thereafter receive 1 dose every 6 months. All dosages are 284 mg. All doses are administered subcutaneously in the abdomen, upper arm, or thigh. The injection should be administered by a healthcare professional.

Warning and Contraindications

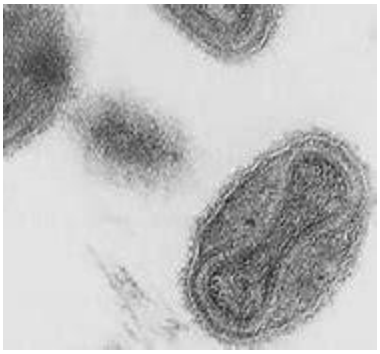
There are no contraindications to inclisiran. Injection site reaction is the most common adverse effect. Overall, adverse reactions led to discontinuation of treatment in 2.5% of patients. This compares to 1.9% of patients who were treated with placebo. As with all agents which lower cholesterol, inclisiran should be discontinued in pregnant patients, as cholesterol-lowering agents affect sex hormones. Inclisiran is present in the breast milk of animals and is assumed to be in the breast milk of humans and therefore, breastfeeding while on inclisiran is generally not recommended but the mother's clinical status can be considered in the decision-making process.

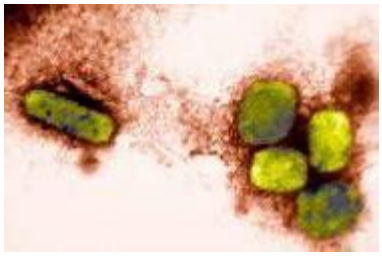
No dosage adjustments are required for the elderly, renal impairment, or hepatic impairment.

In summary, inclisiran is another weapon in the treatment of heterozygous familial hypercholesterolemia in adult patients who are maximally tolerated statin therapy and yet not at a target level for LDL-C Cholesterol. Twice yearly dosing is more convenient for the patient than monthly dosing though the dose must be administered by a healthcare professional which may affect compliance.

References

1. FDA. FDA approves add-on therapy to lower cholesterol among certain high-risk adults | FDA
2. Leqvio Prescribing Information. Physician's Labeling Rule_Content (novartis.com)





FDA approves treatments for both Smallpox and Ebola

Robert Stanton, M.B.A., Pharm.D., BCPS

The FDA approved brincidofovir (Tembexa) for the treatment of smallpox in June of 2021. The disease is considered eradicated in 1980 but drug development continues in case there is a need for medical countermeasure response. Brincidofovir is an oral suspension indicated for smallpox in all age groups. Because of the similarity between smallpox and monkeypox, brincidofovir is being investigated for use in monkeypox though there is no clinical data on the effectiveness against monkeypox at the moment.

The FDA also approved ansuvimab-zykl (Ebanga) for the treatment of Ebola. Ansuvimab-zykl is a monoclonal antibody which blocks binding of the Ebola virus to the cell receptor preventing its entry into the cell. Patients who receive ansuvimab-zykl should avoid receiving live vaccine against Ebola as ansuvimab-zykl will potentially reduce the efficacy of any such vaccine.

1. FDA. FDA approves drug to treat smallpox | FDA
2. CDC. Treatment Information for Healthcare Professionals | Monkeypox | Poxvirus | CDC
3. FDA. FDA approves treatment for ebola virus | FDA

Sexually Transmitted Infections- 2021 Updates

Tyler B. Clay, PharmD, BCPS

Sexually transmitted infections continually hit record highs with 2.5 million new cases of chlamydia, gonorrhea and syphilis being reported in 2019, a record high for the sixth straight year. [1] In response to emerging bacterial resistance trends, the CDC developed a National Strategic Plan in addition to updated guidelines for the treatment of sexually transmitted infections in 2021. This article focuses on pertinent guideline updates for the treatment and prevention of chlamydia, gonorrhea, and syphilis as outlined in the 2021 update.

Chlamydia

Chlamydia is the most commonly reported bacterial STI in the United States with most cases occurring in persons aged 24 years and younger. Following initial diagnosis of *C. Trachomatis* infection, rapid treatment can prevent adverse complications such as progression to Pelvic Inflammatory Disease (PID), continued sexual transmission, and vertical transmission to neonates during birth. **The most recent CDC guidelines recommend Doxycycline 100mg twice daily for seven days as the preferred treatment option[2].**

This change (away from azithromycin as a first line treatment option) comes in response to a meta-analysis and Cochrane systemic review which evaluated clinical response and treatment failure of patients treated with doxycycline in comparison to azithromycin. [3,4] Emerging data suggests azithromycin may be less efficacious in rectal and oropharyngeal C. *trachomatis* infections[5]. Although azithromycin does maintain high efficacy for urogenital *C. trachomatis* infection, rectal infection has been commonly reported in male and female patients with urogenital infections and cannot be accurately predicted by reported sexual activity or sexual orientation. Treatment failure associated with anorectal infection places women at high risk for autoinoculation from anorectal sites, resulting in an increased incidence in recurrent infection and reproductive complications.[6] It should be noted that Azithromycin 1 gram orally as a single dose remains the preferred treatment strategy in pregnancy as doxycycline is contraindicated in the second and third trimesters because of the risk for tooth discoloration. [2]

Gonorrhea

In the United States, an estimated 1,568,000 new *N. gonorrhoeae* infections occur each year, yielding gonorrhea as the second most reported bacterial communicable disease.[2] Additionally, treatment of gonorrhea may often be delayed in female patients as the infection often remains asymptomatic resulting in the increased incidence of antimicrobial resistance. To combat *N. gonorrhoeae* resistance, the Gonococcal Isolate Surveillance Project (GISP) was established. This GISP has played an instrumental role in shaping the treatment recommendations for gonorrhea including the recommendation away from fluoroquinolone treatment in 2007, leaving cephalosporins as the only remaining class of antimicrobials for the treatment of gonorrhea in the United States. Because of further resistance concerns, the 2010 CDC STD treatment guidelines recommended dual therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline. Although recommendations for dual therapy are felt to have mitigated the emergence of reduced susceptibility to ceftriaxone, concerns regarding potential harm to the microbiome and the effect on other pathogens have driven 2021 guideline directed treatment away from dual therapy.[7] **Consequently, ceftriaxone 500mg IM as a single dose for patients weighing less than 150kg and 1000mg IM as a single dose for patients exceeding 150kg are now the recommended regimens. [2]**

Syphilis

From 2012 to 2019, congenital syphilis rates in the United States increased from 8.4 to 48.5 cases per 100,000 births, a 477.4% increase. Syphilis treatment has been divided into stages on the basis on clinical findings. Primary syphilis most commonly presents as a single painless ulcer or chancre at the site of infection but may also present as multiple, atypical more painful lesions .[8] Secondary syphilis manifestations may include skin rash, mucocutaneous lesions and lymphadenopathy. Tertiary syphilis may present with cardiac involvement, gummatous lesions, tabes dorsalis, and genital paresis. Latent infections without clinical manifestations must be identified through serologic testing. [2]

Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (first visit in the second trimester or later) methamphetamine or heroin use, incarcerated women, or partners, and those with unstable housing or homelessness. Currently, guidelines recommend syphilis screening for all pregnant females at the first prenatal visit regardless of risk factors or previous testing.[9] Current guidelines recommend parenteral penicillin G for treating all stages of syphilis, including cases associated with pregnancy. [2] Selection of the appropriate formulation of penicillin is essential based on the diagnostic staging to ensure the formulation selected has adequate penetration to the sites associated with the type of infection diagnoses. Current guidelines endorse a single dose of benzathine penicillin 2.4 million units IM for adults with primary and

secondary syphilis. Evidence has suggested that additional therapy is beneficial for pregnant women to prevent congenital syphilis. For pregnant women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G2.4 million units can be administered 1 week after the initial dose. Guidance for the management of adults with latent, tertiary, or neurosyphilis can be found at https://www.cdc.gov/mmwr/volumes/70/rr/rr7004a1.htm . Combination products of benzathine penicillin, procaine penicillin, and oral penicillin formulations are not considered appropriate for syphilis treatment.

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Substitution of Biological Pharmaceuticals:

What prescribers can expect from pharmacists

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The following quick review was pulled from Title 15 Legislature Rule West Virginia Board of Pharmacy Series 17 Board of Pharmacy Rules for the Substitution of Biological Pharmaceuticals found on pages 229-232 of the 2021 Pharmacy Laws and Legislative Rules of West Virginia.

- **Select Definitions:**
  - **§**15-17-2.1 Biological product
    - "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative or arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings"
  - **§ 15-17-2.2** Biosimilar
    - "a biological product that has been licensed as a biosimilar…reflecting that it is highly similar to the specific reference biological product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the reference biological product in terms of safety, purity, and potency of the product."
  - **§15-7-2.4** Interchangeable biologic product
    - "a biological product that the federal Food and Drug Administration has licensed and determined meets the standards for interchangeability or determined is therapeutically equivalent as set forth in the latest edition of or supplement of the federal Food and Drug Administration's Approved Drug Products with Therapeutic Equivalence Evaluations."
  - **§15-7-2-7** Reference biological product
    - "the single biological product licensed against which a biological product is evaluated in an application submitted to the U.S. Food and Drug Administration for licensure of biological products as biosimilar or interchangeable"
- **§15-7-3 Substitution Requirements**
  - Pharmacists must utilize the Lists of Licensed Biological Products with Reference Product Exclusivity or Bi similarity or Interchangeability Evaluations (also known as the Purple Book) when evaluating interchangeability
  - The following criteria must be met before a pharmacist may dispense an interchangeable biologic:
    - The interchangeable biologic product cannot cost more than the originally prescribed product.
    - The patient must agree to the substitution.
    - Brand medically necessary has not been specified by the practitioner.
      - Note: All refills must follow the original substitution instructions, unless otherwise indicated.
- **§15-7-4 Patient Notification**
  - The patient/patient's agent, must be informed that a "less expensive interchangeable biologic product is available." The patient will then choose the interchangeable biologic product, or the brand prescribed.
- **§15-7-5 Communication with prescribers**

- The dispensing pharmacy must contact the prescriber no later than the 5th business day after the date of dispensing regarding the specific product provided to the patient (including the name of the product and the manufacturer or NDC number).
- Communication is not required if there is no interchangeable biologic product or when the product is being refilled with the same product previously dispensed.

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