Evidence-Based Drug Therapy Update

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Objectives

- Recognize the indications and adverse effects for new medications
- Describe the mechanism of action and place in therapy for new medications
- Determine the place in therapy for newly approved medications

FDA Approval Process

- https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf

FDA Approval Process

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Special Circumstances

Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
• Fulfills an unmet medical need for serious conditions • Can be based on "promising" animal or human data	• Treats a serious condition and preliminary evidence suggests a substantial benefit over currently available therapies	• Action taken within 6 months for drugs that would significantly improve treatment of serious conditions • Standard review is 10 months	• Fulfills an unmet medical need for a serious condition • May use surrogates or intermediate clinical endpoints

https://www.fda.gov/drugs/developmentapprovalprocess/default.htm

"Follow On Biologics"

Reproducing biologics is complex→ term "generic" deemed inappropriate by FDA

No clear pathway existed to approve "generic" versions of biologics

- 1944: Public Health Service Act (PHSA)
  - Full clinical trials needed to approve new drugs or biologics
- 1984: Hatch-Waxman Act
  - Generic drugs allowed, did not address biologics

2010: Biologics Price Competition and Innovation Act (BPCIA)

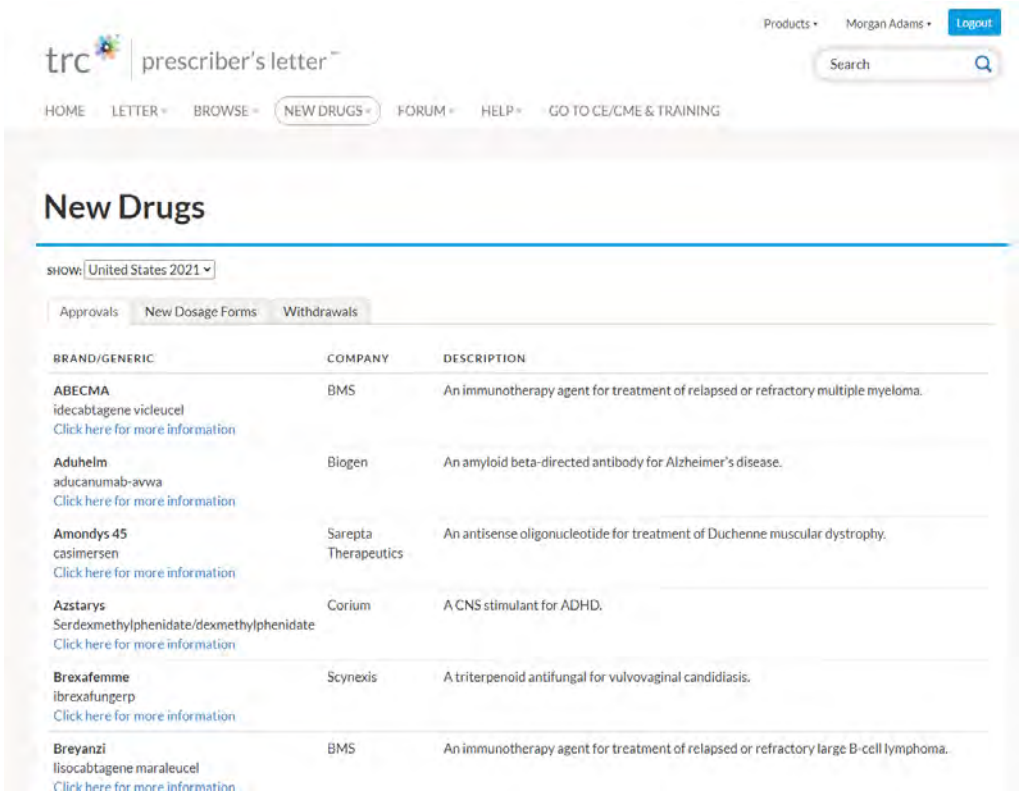
- Biologics allowed if **safety (including immunogenicity) and efficacy comparable to reference product** (original brand)

CRS Report for Congress

US Pharm. 2009;34(6):22-23.

Keeping Up with New Drugs

- FDA website
  - https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm
- Prescriber's Letter/Medical Letter
- MyDailyMed
- AAFP STEPS review



- Safety
- Tolerability
- Efficacy
- Price
- Simplicity

STEPS

New Drug Reviews

Sofosbuvir/Velpatasvir (Epclusa) for Hepatitis C

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STEPS new drug reviews cover Safety, Tolerability, Effectiveness, Price, and Simplicity. Each independent review is provided by authors who have no financial association with the drug manufacturer.

The series coordinator for *AFP* is Allen F. Shaughnessy, PharmD, MMedEd, Contributing Editor.

A collection of STEPS published in *AFP* is available at http://www.aafp.org/afp/steps.

Sofosbuvir/velpatasvir (Epclusa) is an oral medication labeled for the treatment of adults who have chronic infection with hepatitis C virus (HCV) genotypes 1 through 6. Unlike elbasvir/grazoprevir (Zepatier) and ledipasvir/sofosbuvir (Harvoni), sofosbuvir/velpatasvir can be used to treat patients with genotypes 2 and 3. It is also labeled for use in combination with ribavirin to treat patients with decompensated cirrhosis (Child-Pugh score of B or C).[1,2]

Drug	*Starting dosage*	*Dose form*	*Cost**
Sofosbuvir/velpatasvir (Epclusa)	One tablet per day for 12 weeks	400-mg/100-mg tablet	$75,000 for a 12-week course

**—Estimated retail price of one month's treatment based on information obtained at http://www.goodrx.com (accessed March 27, 2017).*

SAFETY

The main safety concern with sofosbuvir/velpatasvir is reactivation of hepatitis B virus (HBV) in coinfected patients, which is unusual but may happen with any treatment of HCV infection. All patients should be tested for HBV before starting therapy by measuring hepatitis B surface antigen (HBsAg) and anti–hepatitis B core (anti-HBc) antibody. Patients with serologic evidence of HBV infection should be monitored for clinical and laboratory signs of hepatitis flare-up or HBV reactivation during treatment and posttreatment follow-up.[1,2]

Sofosbuvir/velpatasvir affects or is affected by numerous medications, and a suitable drug interaction reference should be consulted before beginning treatment or when considering additional medications during treatment.[1,2] Liver enzyme inducers such as rifampin, St. John's wort, and carbamazepine (Tegretol), along with others, will decrease the therapeutic effect of sofosbuvir/velpatasvir. Proton pump inhibitors should not be taken with sofosbuvir/velpatasvir; histamine H_2 receptor blockers and antacids may be used, but there are specific timing guidelines in the product labeling. Interactions with antiarrhythmics (especially amiodarone) and anticonvulsants can cause significant adverse effects. Sofosbuvir/velpatasvir has not been studied in pregnant or breastfeeding women.[1]

TOLERABILITY

Sofosbuvir/velpatasvir is generally well tolerated, with only 0.2% of patients discontinuing treatment in clinical trials because of adverse effects. Fatigue and headaches are the most commonly reported adverse effects.[1]

EFFECTIVENESS

Among patients without cirrhosis or with compensated cirrhosis, 95% to 99% will achieve sustained virologic response (defined as HCV RNA less than 15 IU per mL at 12 weeks after completion of treatment; sustained virologic response is only a biomarker for cure of HCV infection and does not imply direct effects on morbidity or mortality). In one small study comparing sofosbuvir/velpatasvir (n = 64) with placebo (n = 116) in patients with HCV genotypes 1, 2, 4, 5, and 6, 99% of the patients taking sofosbuvir/velpatasvir achieved sustained virologic response vs. none of the patients treated with ▸

placebo.[1,3] In patients with HCV genotype 3, sofosbuvir/velpatasvir is more effective than sofosbuvir/ribavirin, with response rates of 95% vs. 80%, respectively.[1,4]

In patients with decompensated cirrhosis (Child-Pugh score of B), 94% will achieve sustained virologic response when treated with sofosbuvir/velpatasvir in combination with ribavirin.[1,5] There are no studies comparing the effectiveness of sofosbuvir/velpatasvir with elbasvir/grazoprevir or ledipasvir/sofosbuvir.

PRICE

A complete 12-week course of sofosbuvir/velpatasvir will cost approximately $75,000. This price is in the same range as elbasvir/grazoprevir ($60,000 for a 12-week course; $80,000 for a 16-week course) and ledipasvir/sofosbuvir ($94,000 for a 12-week course). Adding 12 weeks of ribavirin (1,000 mg per day) will cost approximately $550 to $850 more.[2]

SIMPLICITY

Sofosbuvir/velpatasvir is taken orally once daily with or without food. It does not require adjustment for renal or hepatic disease.

Bottom Line

Sofosbuvir/velpatasvir is an effective treatment for patients with HCV and has minimal adverse effects. It is the preferred treatment for patients with genotype 2 or 3. As with other curative treatments, it is very expensive. Patients should be instructed to avoid using proton pump inhibitors and only take antacids and H_2 blockers if timed appropriately during treatment.

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Author disclosure: No relevant financial affiliations.

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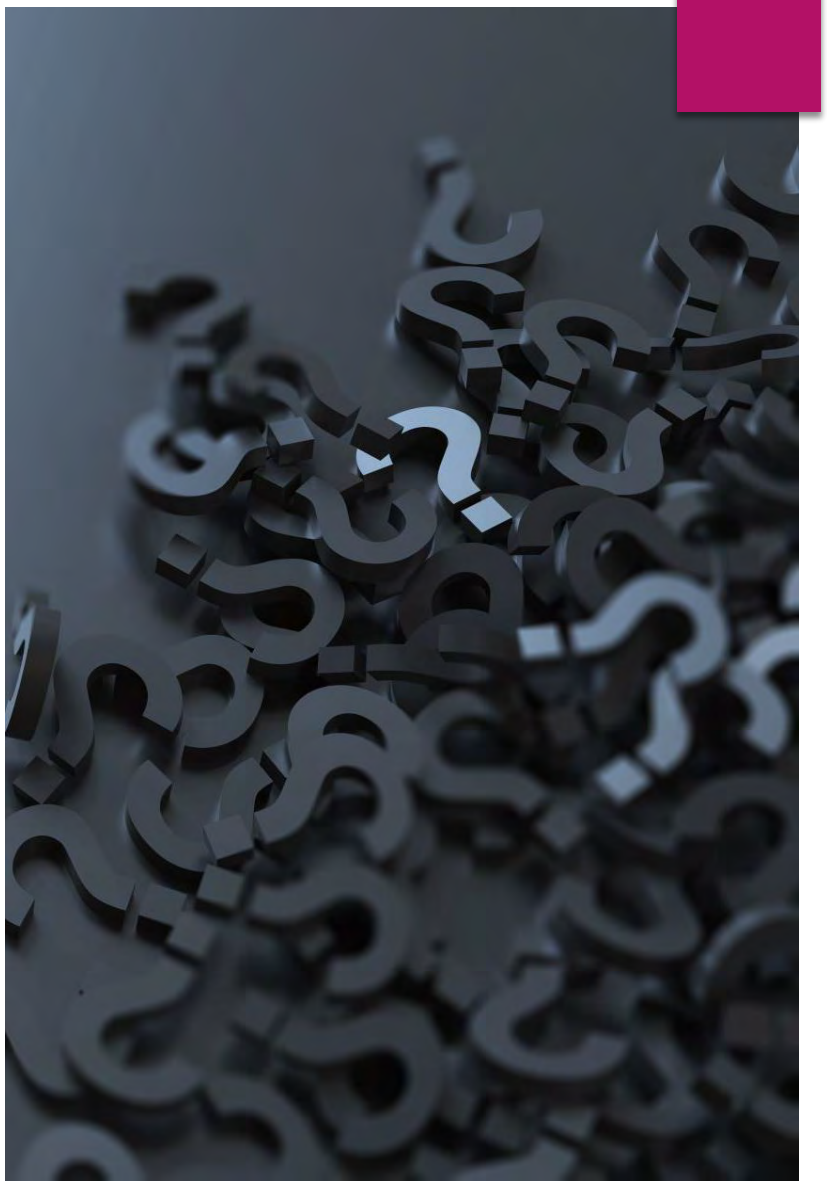
2. Centers for Disease Control and Prevention, University of Washington, The University of Alabama at Birmingham, The International Antiviral Society–USA. Hepatitis C online. http://www.hepatitisc.uw.edu/. Accessed March 12, 2017.
3. Feld JJ, Jacobson IM, Hézode C, et al.; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015;373(27):2599-2607.
4. Foster GR, Afdhal N, Roberts SK, et al.; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med.* 2015;373(27):2608-2617.

New Drugs

Reflections on New Meds

- Which of these will you consider integrating into your practice?
- Which of these is the most "game-changing" and why?



2023…

THE YEAR OF RSV

RSV (Arexvy®)

FDA Approval:

- Prevention of lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older
  - Reduced risk of developing lung disease from RSV by 82.6%
  - Reduced risk of severe lung disease from RSV by 94.1%

Type of vaccine

- Lyophilized recombinant , adjuvanted antigen vaccine

Dosing: 0.5 mL IM once

Arexvy package insert

Types of Vaccines

Type of Vaccine		Examples
Live	Attenuated	• MMR • Varicella • Influenza nasal • Rotavirus • Zoster (Zostavax) • Yellow Fever • Typhoid
Inactivated	Killed	• Polio • Hepatitis A • Rabies
	Subunit/conjugate	• Pertussis • Hepatitis B • Influenza • Pneumococcal • Meningococcal • Human papillomavirus
	Toxoid	• Diptheria/tetanus
	Adjuvanted	• Fluad • Zoster (Shingrix)
	mRNA	• Pfizer & Moderna Covid vaccines

Adjuvanted--> to aid
Enhances immune response

Respiratory Syncytial Virus Prefusion F Protein Vaccine

Phase 3, RCT comparing RSVPreF3 to placebo
25,040 patients, adults ≥ 60 in 17 countries
At 6.7 month follow up:

- RSV-related lower resipiratory tract infections
  - Placebo (40/12,494) vs RSVPreF3 (7/12,466)
  - Vaccine efficacy 82.6% (96.95%CI 57.9-94.1)

Side effects:

- Any: 71.9% RSVPreF3 vs 27.9% placebo
- Pain: 60.9% RSVPreF3 vs 9.3% placebo
- Fatigue: 33.6% RSVPreF3 vs 16.1%

RSV (Abryso®)

FDA approval:

- Prevention of lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older
- Pregnant patients at 32 through 36 weeks gestational age for the prevention of lower respiratory tract disease from RSV in infants from birth through 6 months of age

Type of vaccine

- Lyophilized recombinant antigen vaccine
  - Note: no adjuvant --> lower efficacy than Arexvy®
- Provides active and passive immunity in pregnancy

RSV (Abryso®)

Efficacy:

- Pregnancy:
  - 34.7% (90 days)/57.3% (180 days) for infants 0-6 months for any lower respiratory tract disease from RSV
  - 91.1% (90 days)/76.5% (180 days) for infants 0-6 months for severe respiratory disease from RSV
- Adults 60+
  - 66.7% in patients with 2+ RSV symptoms

Cost: ~$320

Adverse reactions:

- Pregnancy: injection site pain (40.6%), headache (31.0%), muscle pain (26.5%), and nausea (20.0%)
- Patients 60+: fatigue (15.5%), headache (12.8%), injection site pain (10.5%), and muscle pain (10.1%)

Abryso package insert

RSV (Abryso®) in Adults ≥60

Phase 3, RCT comparing RSVPreF vs placebo in patients ≥60

34, 284 patients in multiple countries

- Immunocompromised patients excluded

Efficacy data:

- RSV-associated lower respiratory tract illness with ≥2 symptoms: 66.7% efficacy
  - §11 cases in RSVPreF vs 33 in placebo
- RSV-associated lower respiratory tract illness with ≥3 symptoms: 85.7% efficacy
  - §2 cases in RSVPreF vs 14 in placebo

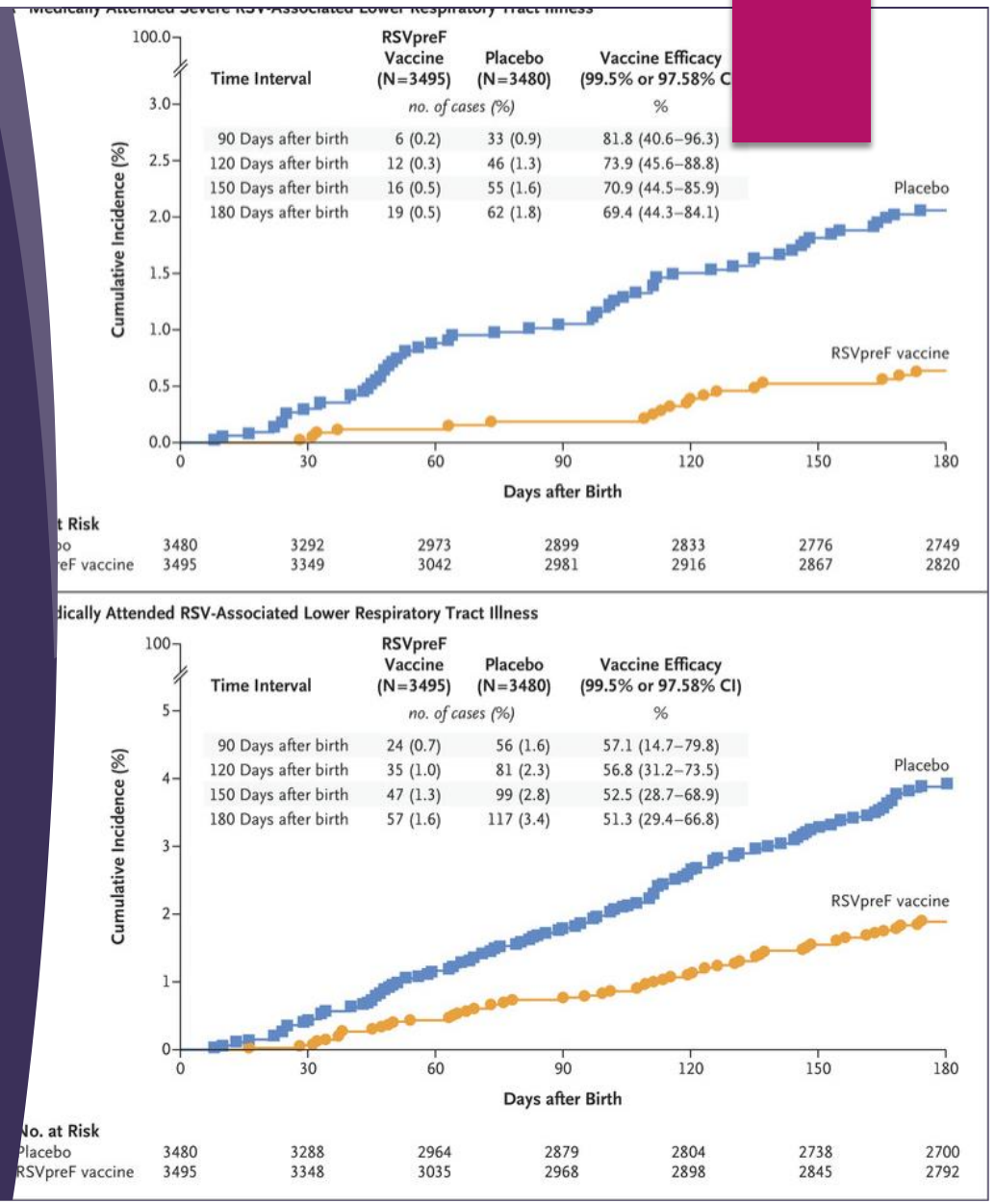
Safety data:

- Local reaction within 7 days: 12% in RSVPreF vs 7% in placebo
- Systemic reaction within 7 days: 27% in RSVPreF vs 26% in placebo
- Any adverse event within 1 month: 9$ vs 8.5% in placebo

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults | NEJM

RSV (Abryso®) in Pregnancy

- Phase 3, RCT comparing RSVPreF to placebo in uncomplicated singleton pregnant patients at 24-36 weeks gestation to prevent RSV illness in infants
- 7392 patients
  - High risk pregnancies excluded



https://www.nejm.org/doi/full/10.1056/NEJMoa2216480

RSV (Abryso®) in Pregnancy

Safety data

- Maternal participants: ≥1 adverse event within 1 month
  - Any side effect: 13.8% RSVPreF vs 13.1% placebo
  - Serious: 4.2% RSVPreF vs 3.7% placebo
  - Severe: 1.7% RSVPreF vs 1.3% placebo
- Infant participants: ≥1 adverse event within 1 month
  - Any side effect: 37.1% RSVPreF vs 34.5% placebo
  - Serious: 15.5% RSVpreF vs 15.2% placebo
  - Severe: 4.5 RSVpreF vs 3.8% placebo

The New York Times

Some Pregnant Women and Infants Received the Wrong R.S.V. Shots

Doctors and pharmacists seem to be confused by the guidelines. And the brand names aren't helping.

Share full article

At least 128 pregnant women and at least 25 young children got R.S.V. vaccinations that they should not have received, according to the C.D.C. Swen Pförtner/picture alliance, via Getty Images

https://www.nejm.org/doi/full/10.1056/NEJMoa2216480

RSV Vaccine: CDC Schedule

Included on SC Board of Pharmacy Protocol to administer to patients WITHOUT a prescription

Pregnancy:

- 1 dose 32 weeks 0 days through 36 weeks and 6 days gestation from September through January
- Abryso®

Patients 60 and older:

- Shared decision making
- Consider for patients at high risk of severe RSV disease (i.e. lung disease, cardiovascular disease, kidney disease, etc.)
- Arexvy® or Abryso®

Respiratory Syncytial Virus (RSV)	**Seasonal administration during pregnancy. See Notes.**		**≥60 years**

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-

Nirsevimab (Beyfortus®)

CDC Recommendations

- 1 dose within 1 week of birth for children born during RSV season (October-March)
  - Not indicated if mom received RSV vaccine >14 days before delivery
- Infants born outside of RSV season: 1 dose before RSV season
  - Not indicated if mom received RSV vaccine >14 days before delivery
- Immunocompromised, chronic lung disease, etc. ages 8-19 months entering 2nd RSV season: 1 dose before RSV season

https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Nirsevimab (Beyfortus®)

Monoclonal antibody

FDA approval

- Prevent RSV-associated lower respiratory tract disease newborns/infants born during or entering their 1st RSV season up to 24 months

Dosing

- 1st RSV season
  - <5 kg: 50 mg IM x 1 dose
  - >5 kg: 100 mg IM x 1 dose
- At inc'd risk for severe dx during 2nd RSV season (<24 months)
  - 200 mg IM x 1 dose
- Different dosing for patients undergoing cardiac surgery with cardiopulmonary bypass

Beyfortus package insert

Nirsevimab (Beyfortus®)

Prefilled syringes, stored refrigerated

- Cost/availability
- ~$500 for 50 mg and 100 mg doses
- ~$1000 for 200 mg dose
- Comparison to existing product
- Palivizumab (Synagis®) only indicated for high risk infants at beginning of RSV season
  - Hx of premature birth 35 weeks gestational age <6 months
  - Congenital heart disease, bronchopulmonary dysplasia <24 months
  - Cost: ~$2000

Limited Availability of Nirsevimab in the U Stat —Interim CDC Recommendations to Protect Infants from Respiratory Syncytial Virus (RSV) during the 2023–2024 Respiratory Virus Season

Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
October 23, 2023, 3:30 PM ET
CDCHAN-00499

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to provic options for clinicians to protect infants from respiratory syncytial virus (RSV) in the context of a limited supply of nirsevim a long-acting monoclonal antibody immunization product recommended for preventing RSV-associated lower respiratory disease in infants.

In the context of limited supply during the 2023–2024 RSV season, CDC recommends prioritizing available nirsevimab 100 doses for infants at the highest risk for severe RSV disease: young infants (age <6 months) and infants with underlying cor that place them at highest risk for severe RSV disease. Recommendations for using 50mg doses remain unchanged at this Avoid using two 50mg doses for infants weighing ≥5 kilograms (≥11 pounds) to preserve supply of 50mg doses for infants weighing <5 kilograms (<11 pounds). Providers should be aware that some insurers may not cover the cost of two 50mg d for an individual infant.

https://emergency.cdc.gov/han/2023/han00499.asp

https://www.aap.org/en/patient-care/respiratory-syncytial-virus-rsv-prevention/nirsevimab-beyfortus-product--ordering-information/#:~:text=Nirsevimab%20purchase%20cost&text=%24495%20per%20dose%20for%2050mg,200mg%20dose%20(Two%20100mg%20doses)

Nirsevimab (Beyfortus®)

RCT of 8058 infants 12 months or younger in 1st RSV season in France, Germany, or UK

Primary endpoint: hospitalization due to RSV-associated lower respiratory tract infection

- Nirsevimab 0.3% vs placebo 1.5%
  - 83.2% reduction (95% CI, 67.8-92.0%, p<0.001)

Secondary outcomes: very severe RSV-associated lower respiratory tract infection

- Nirsevimab 0.1% vs placebo 0.5%
  - 75.7% reduction (95% CI, 32.8-92.9%, p=0.004

Nirsevimab reduced hospitalization due to RSV-associated lower respiratory tract infection compared to placebo

NEJM. 2023. 389. 2425-35.

Other ID meds

Apretude (cabotegravir)

Long-Acting Injectable Approved for HIV Pre-Exposure Prophylaxis (PrEP)!

Indication: HIV PrEP for adults and adolescents weighing at least 35 kg who are at risk of sexually acquiring HIV (need negative HIV test prior to start)

Dosing: 600 mg (3 mL) injection.
Two initiation injections one month apart, then one injection every 2 months thereafter.

Optional 1 month lead-in with oral cabotegravir

Supplied as white/light pink suspension in vial, no reconstitution needed. Gluteal intramuscular injection administered by healthcare professional.

@AmbCareRx

Apretude (cabotegravir)

Apretude (cabotegravir)

- Side Effects (>1%): injection site reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgia, rash, decreased appetite, somnolence, back pain, and upper respiratory tract infection
- Cost: ~$5,600/month
- Place in therapy
  - Consider for patients to promote adherence

HIV PrEP Abbreviated Implementation Toolkit

PrEP is recommended in the following groups at substantial risk of HIV acquisition:

- Sexually active adult MSM (men who have sex with men)
- Adult heterosexually active men & women
- Adults who inject drugs
- Heterosexual HIV-discordant couples (men & women) to protect the uninfected partner during conception & pregnancy
- Transgender individuals especially black transgender women (MtF)

PrEP medication options

- Daily oral PrEP (approved in adults & adolescents > 35 kg)
  - Truvada (tenofovir disoproxil fumarate [TDF] 300 mg & emtricitabine 200 mg)
  - Descovy (tenofovir alafenamide [TAF] 25 mg & emtricitabine 200 mg) *in MSM & transgender women*
- Cabotegravir (Apretude) IM injection

All provider visits should address symptom history to r/o acute HIV, risk reduction counseling, & condoms

PrEP Orientation Visit	Initial Visit
Discuss PrEP options (including insurance coverage/assistance)	Medication considerations • Oral PrEP: 7 days before adequate drug levels in rectal tissue and 20 days in vaginal tissue/blood • IM PrEP: unknown time to protection, compliance, & side effects 30-day supply of PrEP *start within 7 days of HIV screen*

Labs for daily oral PrEP	Labs for IM cabotegravir
Mandatory baseline labs: - HIV Ab/Ag screen (4th gen POC lab) *must be done prior to prescribing PrEP* - BMP (determine renal function) - Hepatitis Bs Ag/Ab - Lipids (if TAF product)	Mandatory baseline labs: - HIV RNA assay/HIV Ag-Ab - Pregnancy test (as appropriate)
Other baseline labs as indicated: - Hepatitis C antibody - RPR/Trep Ab - Triple site GC/CH testing- urine, rectal, oral based on exposure - Pregnancy test (as appropriate) & offer contraception	Other baseline labs as indicated: - Hepatitis Bs Ag/Ab and cAB - Hepatitis C antibody - RPR/Trep Ab - Triple site GC/CH testing- urine, rectal, oral based on exposure

Follow Up Visits

*STI testing: every 3 months in asymptomatic MSM at high risk of recurrent STIs & in all symptomatic & sexually active

IM Cabotegravir (CAB) Follow Up Visits	
Eligibility	- Weigh ≥ 35 kg - Negative HIV-1 infection
Day 0	- Administer gluteal IM CAB 600 mg injection or prescribe daily oral CAB lead-in for 4 weeks - Injection site reaction: may have transient reaction for 2-3 days following first 2 or 3 shots. Use OTC pain meds & warm compress
1 month visit	- HIV Ab/Ag Test + HIV RNA assay required - Administer 2nd dose 600 mg IM CAB
Every 2-month visit (starting at Month 3)	- HIV Ab/Ag Test + HIV RNA assay required every two months - Administer IM CAB in office
4-month visit	- RPR/Trep Ab and GC/CH triple site in MSM/TGW
6-month visit	- RPR/Trep Ab and GC in hetero
12-month visit	- In MSM/TGW: RPR/Trep Ab and GC/CH triple site - In hetero: RPR/Trep Ab and GC/CH
After 12-month visit	- Re-evaluate need for continuing PrEP - When stopping, get HIV RNA assay

Vivjoa (oteseconazole)

- FDA approval
  - Reduces incidence of recurrent vulvovaginal candidiasis in females NOT of reproductive potential
- Mechanism of action
  - Azole antifungal

Vivjoa-only	Fluconazole/Vivjoa
Day 1: 600 mg	Day 1, 4, 7: fluconazole 150 mg
Day 2: 450 mg	Days 14-20: oteseconazole 150 mg daily
Starting day 14: 150 mg weekly for 11 weeks	Starting day 28: oteseconazole 150 mg weekly for 11 weeks

Vivjoa (oteseconazole)

- Side effects
  - Headache, nausea
- Cost: $2700/course of therapy
  - Compare to fluconazole $4/tablet
- Place in therapy
  - Only for postmenopausal or permanently infertile women with 3 + yeast infections
    - Teratogen in animals → will stay in body for up to 2 years!
  - Last resort!
  - Other options for recurrent yeast infections
    - Vaginal clotrimazole x 7 days, then 2 x/week for 6 months
    - PO fluconazole every 3 days for 3 doses, then weekly for 6 months
    - Boric acid vaginal suppositories

Psych drugs

Brixadi (Weekly SQ and Monthly SQ Buprenorphine)

- FDA approval
  - Moderate to severe opioid use disorder
  - AFTER tolerating at least 1 dose of SL buprenorphine
- Mechanism of action
  - Partial mu opioid agonist
- Dosing: 24-32 mg/week, adjusting doses weekly
- Administration
  - Only by health care professional, only delivered to a health care facility
  - Slow SQ into buttock, thigh, abdomen or upper arm
    - Only use upper arm after 4 doses if buprenorphine-naïve
    - Rotate injection sites

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; BRIXADI RISK EVALUATION AND MITIGATION STRATEGY

- Serious harm or death could result if administered intravenously. BRIXADI forms a liquid crystalline gel upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life-threatening pulmonary emboli, if administered intravenously.
- Because of the risk of serious harm or death that could result from intravenous self-administration, BRIXADI is only available through a restricted program called the BRIXADI REMS. Healthcare settings and pharmacies that order and dispense BRIXADI must be certified in this program and comply with the REMS requirements.

Examples of Patented REMS Programs and Their Characteristics.

Drug	Manufacturer	Indication	Selected Safety Concerns	REMS Program	REMS Highlights	REMS Patent Expiration Dates*
Alvimopan (Entereg)	Cubist	Bowel-resection surgery with primary anastomosis	Myocardial infarction	Entereg Access Support and Education	Hospital enrollment and protocol implementation to ensure that no patient receives >15 doses and the hospital will not dispense the drug for outpatient use	2030
Sodium oxybate (Xyrem)	Jazz	Narcolepsy	Respiratory and central nervous system depression, diversion	Xyrem Success Program	Physician and patient enrollment, dispensing through a central pharmacy using a centralized database	2022–2024
Thalidomide (Thalomid)	Celgene	Multiple myeloma, leprosy	Birth defects, venous thromboembolism	Thalomid REMS	Physician and pharmacy certification; patient counseling, surveys, and pregnancy testing; and 4-wk limited supply with no automatic refills	2018–2020
Pomalidomide (Pomalyst)	Celgene	Multiple myeloma	Birth defects, venous thromboembolism	Pomalyst REMS		
Lenalidomide (Revlimid)	Celgene	Multiple myeloma, transfusion-dependent anemia, mantle-cell lymphoma	Birth defects, venous thromboembolism	Revlimid REMS		

* Expiration dates were obtained from the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") resource.

Element to assure safe use	Example
Health care providers who prescribe the drug have specific training/experience or be specially certified	Prescribers may be required to become certified and/or take training prior to prescribing the REMS drug. As part of the certification, prescribers may need to enroll in the REMS and agree to carry out certain activities for safe drug use. For example, a prescriber may be required to agree to counsel their patients about the particular risk or agree to enroll and/or monitor patients throughout the treatment course.
Pharmacies, practitioners, or health care settings that dispense the drug may be specially certified	Pharmacies, practitioners, or other health care settings that may dispense REMS medications may be required to take the training, train staff, and oversee all processes and procedures needed to implement the REMS requirements. For example, a pharmacy may need to put a process in place that includes verifying that the prescriber of a REMS drug is certified, patients are enrolled, and that laboratory testing or other certain safe use conditions have been carried out prior to dispensing the drug.
Drug be dispensed only in certain health care settings such as hospitals	FDA may require that a REMS drug be dispensed or administered only in a particular setting. For example, a drug may need to be administered or dispensed only in health care settings that have immediate access on-site to supplies and personnel trained to manage a particular adverse event.
Drug be dispensed with evidence of safe-use conditions such as laboratory test results	FDA may require that a REMS drug be dispensed with evidence of safe use conditions. One example of a safe use condition involves ensuring that health care providers and patients have signed a patient-prescriber agreement for a drug that can cause birth defects, so they understand the risk and the need to verify a negative pregnancy test before the drug is dispensed to those patients who could potentially be pregnant.
Each patient using the drug be subject to monitoring	FDA may require that patients using the drug are subject to certain monitoring during and/or after treatment. For example, patients may need to have periodic vision monitoring if the drug is associated with the risk of vision loss.
Each patient using the drug be enrolled in a registry	In certain REMS, patients who take the REMS drug may be required to be enrolled in a patient registry. The patient registry may include all patients enrolled or a subset of all enrolled patients that experience the adverse event of concern. The purpose of a patient registry is to follow patients during and in some cases after treatment with the drug

What is a REMS Drug?

Brixadi Dosing: Buprenorphine-naive

4 mg SL test dose

If tolerated without precipitated withdrawal--> 16 mg/week dose

Give 8 mg within 3 days of 1st dose to achieve recommended 24 mg/week

May give additional 8 mg week 1 (at least 24 hours after previous injection) for totally weekly dose of 32 mg

Brixadi Dosing: Buprenorphine-experienced

Daily dose of sublingual buprenorphine	BRIXADI (weekly)	BRIXADI (monthly)
≤ 6 mg	8 mg	--
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Supporting Primary Prevention

To eliminate unnecessary initial exposure and inappropriate prolonged prescribing of substances with abuse potential, FDA is:

- Promoting appropriate prescribing of medications with abuse potential, including opioids, stimulants, and benzodiazepines
- Exploring the need for potential new authorities for opioid approval standards
- Supporting development of alternative, non-addictive therapies and technologies
- Evaluating innovative packaging and disposal solutions of medications with abuse potential

USG Partners: HHS, CDC, CMS, NIH, SAMHSA

Encouraging Harm Reduction

To reduce morbidity and mortality associated with overdoses, FDA is:

- Expanding availability and access to overdose reversal products, including naloxone, by supporting accelerated review of products and exploring over-the-counter access
- Supporting development of novel overdose reversal products
- Supporting development and authorization of fentanyl test strips to test human specimens at the point of care

USG Partners: HHS, CDC, CMS, IHS, NIH, SAMHSA

Advancing Evidence-Based Treatments

To expand therapy options, availability, and access, FDA is:

- Expanding availability and access to evidence-based treatments for substance use disorders
- Facilitating development of treatments for substance use disorders, with focus on stimulant use disorder
- Facilitating opportunities to incorporate stakeholder engagement into treatment development

Protecting the Public from Unapproved, Diverted, or Counterfeit Drugs Presenting Overdose Risks

To enhance the security of the U.S. drug supply chain, FDA is:

- Preventing and reducing counterfeit and illegal online sales
- Instituting enhanced targeting and screening methods at International Mail Facilities, Express Couriers, and Ports of Entry
- Taking compliance and enforcement actions against unapproved, diverted, or counterfeit drug products

Brixadi (Weekly SQ and Monthly SQ Buprenorphine)

APPROVED AS PART OF THE FDA'S OVERDOSE PREVENTION FRAMEWORK

Buprenorphine Options

Table II: Brand Preparations of Buprenorphine Currently Approved in the US.

Type	Buprenorphine	Buprenorphine/Naloxone	Buprenorphine long-acting
Indication	pain	opioid dependence substitution indication	opioid dependence substitution indication
Brands (available doses)	Belbuca (75, 150, 300, 450, 600, 750, or 900 mcg)	Suboxone (2/0.5, 4/1, 8/2, or 12/3 mg)	Sublocade injection (100, 300 mg monthly)
	Butrans (5, 7.5, 10, 15, or 20 mcg/h or a 7-day patch)	Zubsolv (0.7/0.18, 1.4/036, 2.9/071, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg)	Probuphine implant (74.2 mg every six months)
	Buprenex (300 mcg/ml via intramuscular or intravenous administration)	Bunavail (2.1/0.3, 4.2/0.7, 6.3/1 mg)	Brixadi injection (8, 16, 24 or 32 mg weekly; 64, 96, or 128 mg monthly)

*Information based on corresponding package inserts.

Brixadi (Weekly SQ and Monthly SQ Buprenorphine)

- Side effects (>5%): injection site pain, headache, constipation, nausea, injection site erythema, injection site pruritus, insomnia, and urinary tract infection
- Cost
  - "Most patients will be $10 or less"
  - Actual cost ~$460/8 mg
- Other notes
  - Takes ~1 month (weekly) or 4 months (monthly) to achieve steady state --> buprenorphine will be detectable after discontinuation for 1 month (weekly) or 4 months (monthly)
- Place in therapy
  - Love to have options that promote adherence for patients with SUD
    - Could be an option for patients in "clean living" facilities
  - Must have a DEA license at the clinic to administer

Opvee (nalmefene) Nasal Spray

FDA approval

- Emergency treatment of opioid (natural or synthetic) overdose in patients 12 and older

Mechanism of action

- Opioid antagonist

Dose:

- 2.7 mg, may repeat every 2-5 minutes

Opvee (nalmefene) Nasal Spray

- Cost: $75/2 pack
  - As reference, OTC naloxone ~$50/2 pack
- Place in therapy
  - Lasts longer (up to 6 hours) than naloxone
  - ?May require less doses than naloxone for fentanyl
  - ?Better prevention of respiratory depression at 5 min for remifentanil overdose

Quviviq (daridorexant)

- FDA approval
  - Adults with insomnia (sleep onset and maintenance)
- Mechanism of action
  - Orexin receptor antagonist
    - Blocks wake promotion
- Dosing
  - 25-50 mg 30 minutes before bed
  - Must be able to sleep for 7+ hours

Table 2

Summary of FDA-Approved Orexin Receptor Antagonists

	Suvorexant	Lemborexant	Daridorexant
Dosage form and strength	Tablets: 5 mg, 10 mg, 15 mg, 20 mg	Tablets: 5 mg, 10 mg	Tablets: 25 mg, 50 mg
Metabolism	Hepatic: CYP3A4 (major), CYP2C19 (minor)	Hepatic: CYP3A4/5	Hepatic: CYP3A4
Onset	30 min	<30 min	<30 min
T_{max}	2 h; delayed by high-fat meal	1-3 h; delayed by high-fat meal	1-2 h; delayed by high-fat meal
Excretion	Feces: 66%; urine: 23%	Feces: 57.4%; urine: 29.1%	Feces: 57%; urine: 28%
Half-life	12 h	5 mg: 17 h; 10 mg: 19 h	8 h
Initial dose	10-20 mg	5-10 mg	25-50 mg
Dose in elderly	10-20 mg	5-10 mg	25-50 mg

T_{max}: time to reach maximum concentration.
Source: References 5-11, 13-17, 23, 43.

Quviviq (daridorexant)

- Cost
  - ~$500/month
- Place in therapy
  - Limited—similar to other meds on the market

Pharmacist's Letter
a trchealthcare brand

Quell Hype About New Quviviq for Insomnia

You'll hear **buzz about Rx *Quviviq* (daridorexant) for insomnia**.

It's a me-too orexin antagonist...in the same family as *Belsomra* (suvorexant) and *Dayvigo* (lemborexant). All are C-IVs.

Quviviq will be touted to help patients fall asleep faster...stay asleep longer...and feel less tired during the day. Reps will also say it can be used nightly...with no max duration.

But *Quviviq* only reduces time to fall asleep by about 10 min and increases total sleep time by about 15 min...similar to *Belsomra* or *Dayvigo* and in the ballpark of some Z-drugs, such as zolpidem CR.

Plus *Quviviq* doesn't change how most patients feel the next day. And there's no proof that routine use significantly improves sleep.

Quviviq also has warnings similar to other orexin antagonists and Z-drugs...including sleepwalking, sleep driving, and next-day sedation and fall risk, especially in older adults.

On top of that, all orexin antagonists can have other unusual adverse effects (sleep paralysis, etc)...and CYP3A4 interactions.

Continue to follow a stepwise approach to treating insomnia.

Emphasize nondrug measures, such as sleep hygiene (avoiding phones before bed, etc)...muscle relaxation...and deep breathing.

Look for substances that can impact sleep (alcohol, ADHD meds, etc)...and help manage comorbidities, such as pain or depression.

Save sleep meds as an option for a few weeks if insomnia significantly impacts daytime function.

If one is needed, suggest trying melatonin...especially as an alternative to Rx sleep meds. It seems to reduce time to fall asleep by about 10 min...and is usually well tolerated.

Don't jump to *Quviviq* or any orexin antagonist. They cost about $15/dose versus pennies for melatonin.

Use our resource, *Comparison of Insomnia Treatments*, to weigh pros and cons of ramelteon, doxepin, diphenhydramine, etc.

Gepirone (Exxua)

- FDA approval:
  - Treatment of major depressive disorder
- Dosing
  - 18.2 mg daily, can increase to 36.3 on day 4, then 54.5 mg on day 7, then to max dose of 72.6 mg on day 14
  - Must be given with food
- Mechanism of action
  - "Not fully understood"
  - Selective 5HT1A receptor agonist

Gepirone (Exxua)

- Monitoring
  - ECG prior to initiation, during titrations, and periodically due to risk of QTc prolongation
    - Do not start in patients with QTc >450 msec
- Adverse reactions
  - Black box warning (like many other antidepressants) for suicidal ideation and behavior
  - More common: dizziness, nausea, insomnia, abdominal pain, dyspepsia
  - ***Notably absent adverse reactions: sexual dysfunction, weight gain***

Gepirone (Exxua)

Onset ~2 weeks (faster than most other antidepressants)

Approval based on 2 x 8 week randomized, double-blinded, placebo controlled trials in patients 18-69

Statistically significant improvement in Hamilton Depression Rating Scale (HAMD-17)

Open label trial up to 12 months showed lower rate of relapse (24%) compared to placebo (38.7%)

Gepirone (Euxxa)

- Cost: TBD
  - "competitive with other branded antidepressants"
- Place in therapy
  - Depression is hard to treat, nice to have another slightly different MOA in our toolbox
    - Particularly with the low incidence of sexual dysfunction/weight gain, 2 side effects that tend to make people stop taking their antidepressants
    - And it works a little faster
  - Wouldn't be the 1st one I'd go to, but a good option to have

Leqembi (lecanemab-irmb)

FDA approval

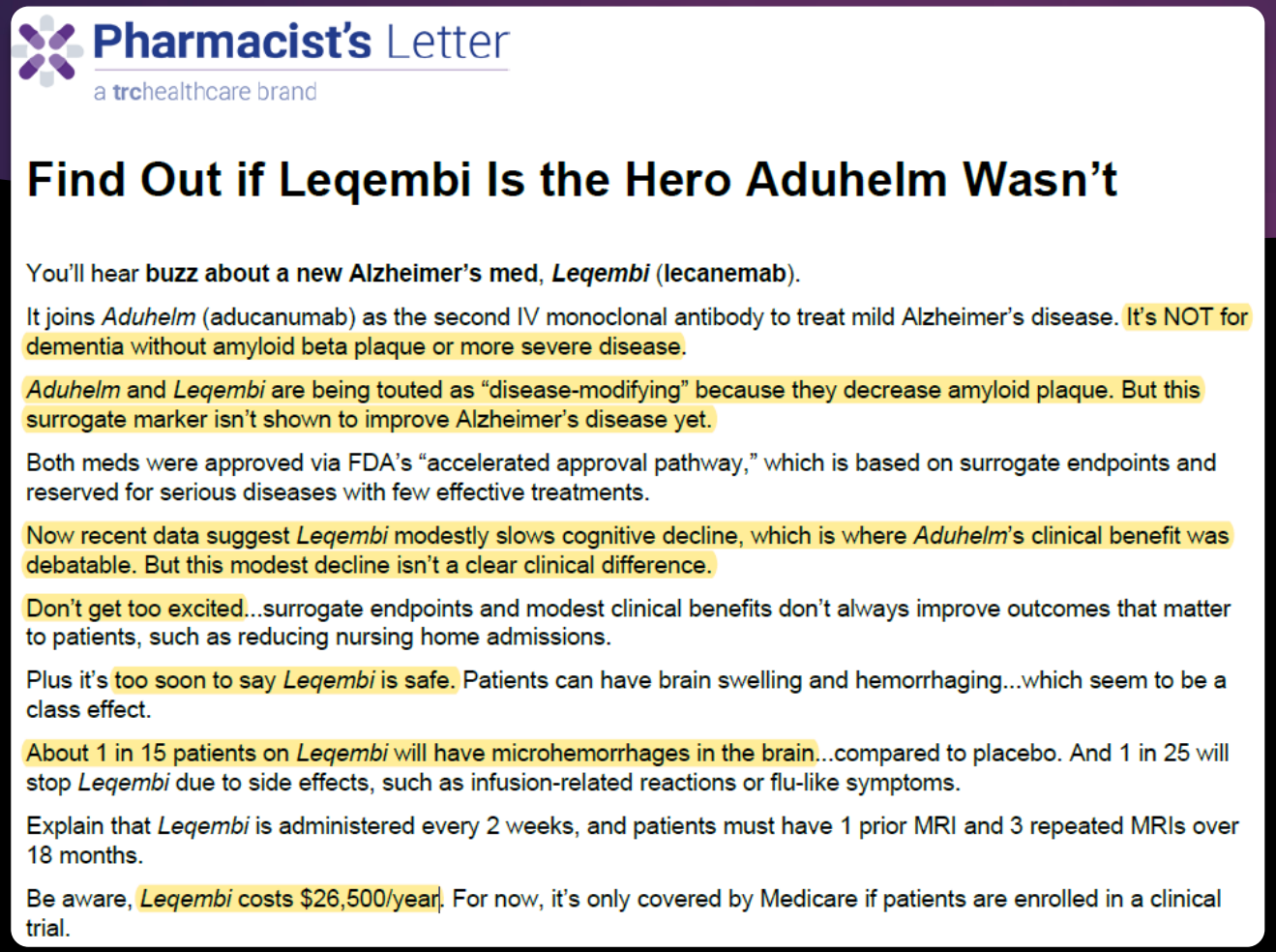
- Treatment of mild Alzheimer's Disease

Mechanism of action

- Monoclonal antibody directed at amyloid beta
  - Amyloid beta plaques in brain pathophysiologic feature of Alzheimer's

Dosing/administration

- 10 mg/kg IV over 1 hour every 2 weeks
  - Must get MRI prior to treatment, then prior to 5th, 7th, and 14th infusions



Pharmacist's Letter

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Find Out if Leqembi Is the Hero Aduhelm Wasn't

You'll hear **buzz about a new Alzheimer's med**, ***Leqembi*** (**lecanemab**).

It joins *Aduhelm* (aducanumab) as the second IV monoclonal antibody to treat mild Alzheimer's disease. It's NOT for dementia without amyloid beta plaque or more severe disease.

Aduhelm and *Leqembi* are being touted as "disease-modifying" because they decrease amyloid plaque. But this surrogate marker isn't shown to improve Alzheimer's disease yet.

Both meds were approved via FDA's "accelerated approval pathway," which is based on surrogate endpoints and reserved for serious diseases with few effective treatments.

Now recent data suggest *Leqembi* modestly slows cognitive decline, which is where *Aduhelm*'s clinical benefit was debatable. But this modest decline isn't a clear clinical difference.

Don't get too excited...surrogate endpoints and modest clinical benefits don't always improve outcomes that matter to patients, such as reducing nursing home admissions.

Plus it's too soon to say *Leqembi* is safe. Patients can have brain swelling and hemorrhaging...which seem to be a class effect.

About 1 in 15 patients on *Leqembi* will have microhemorrhages in the brain...compared to placebo. And 1 in 25 will stop *Leqembi* due to side effects, such as infusion-related reactions or flu-like symptoms.

Explain that *Leqembi* is administered every 2 weeks, and patients must have 1 prior MRI and 3 repeated MRIs over 18 months.

Be aware, *Leqembi* costs $26,500/year. For now, it's only covered by Medicare if patients are enrolled in a clinical trial.

Leqembi (lecanemab-irmb)

A Note on Naming Convention

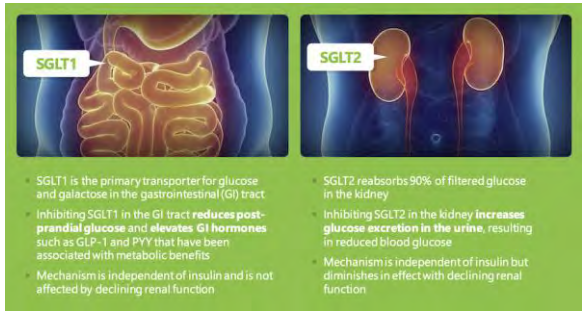
- 2017 FDA Guidance
  - Biologic products must "bear a nonproprietary name that includes an FDA-designated suffix"
    - Suffix must be "devoid of meaning and composed of 4 lowercase letters…attached with a hyphen to the core name"
  - Applies to new biologic products as well as biosimilars and follow-on biologics
  - Aim is to help minimize inadvertent substitutions for products that aren't interchangeable

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

CV Drugs

Inpefa (Sotogliflozin)

- FDA approval
  - Reduce risk of CV death, hospitalization for HF and urgent HF visits for patients with
    - Heart failure (HFpEF and HFrEF)
    - T2DM, CKD or other CV risk factors
- Mechanism of action
  - SGLT1 AND SGLT2 inhibitor
- Dosing
  - 200 mg daily, titrate to 400 mg as needed
- Side effects:
  - UTI, volume depletion, diarrhea, hypoglycemia



Inpefa (Sotogliflozin)

- Cost: ~$600/month (similar to other SGLT2s)
  - Manufacturer completed a cost effectiveness analysis
  - Using $450 for a month's supply found to be cost-effective at about $1,000 a month
- Place in therapy
  - Data supports using in patients recently hospitalized for HF
    - Consider as an option for GDMT
  - Not specifically indicated for diabetes!
  - Definitely do not use if T1DM

Pharmacist's Letter
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Know How Inpefa Stacks Up to Other SGLT2 Inhibitors

New *Inpefa* (sotagliflozin) will try to compete with other SGLT2 inhibitors (*Farxiga*, *Jardiance*, etc).

Inpefa is NOT approved for managing type 2 diabetes yet...although A1c lowering seems similar to other SGLT2 inhibitors.

Instead, expect reps to tout *Inpefa* to reduce heart failure risk...especially for patients with a recent HF hospitalization.

In patients with type 2 diabetes hospitalized for HF, adding *Inpefa* within a couple days of discharge prevents HF urgent care visits, hospitalizations, or CV death in about 1 in 6 patients over 9 months.

But don't think of *Inpefa* as having any advantage over other SGLT2 inhibitors.

For example, data also support starting *Jardiance* (empagliflozin) in stabilized patients with HF before discharge.

Plus *Farxiga* (dapagliflozin) and *Jardiance* have more evidence overall for improving HF outcomes...including over a longer period of follow-up AND in HF with preserved ejection fraction.

And *Inpefa* costs about $600/month...similar to the others.

Caution about key risks with any SGLT2 inhibitor...genital yeast infections, volume depletion, rare Fournier's gangrene, etc.

But be aware, *Inpefa* also increases risk of diarrhea...possibly because it blocks SGLT1 in the gut more than other meds in this class.

Don't jump to *Inpefa*. Continue to recommend an SGLT2 inhibitor based on indication and payer preference.

For example, think about ADDING an SGLT2 inhibitor for patients with symptomatic heart failure with reduced ejection fraction despite optimized triple therapy. Benefits are likely a class effect.

Keep in mind, SGLT2 inhibitors can be started down to an eGFR of 20 mL/min/1.73 m^2 for HF benefits...and continued until dialysis starts.

For a deeper dive into the evidence for SGLT2 inhibitors, see our resource, *Diabetes Medications: Cardiovascular and Kidney Impact*.

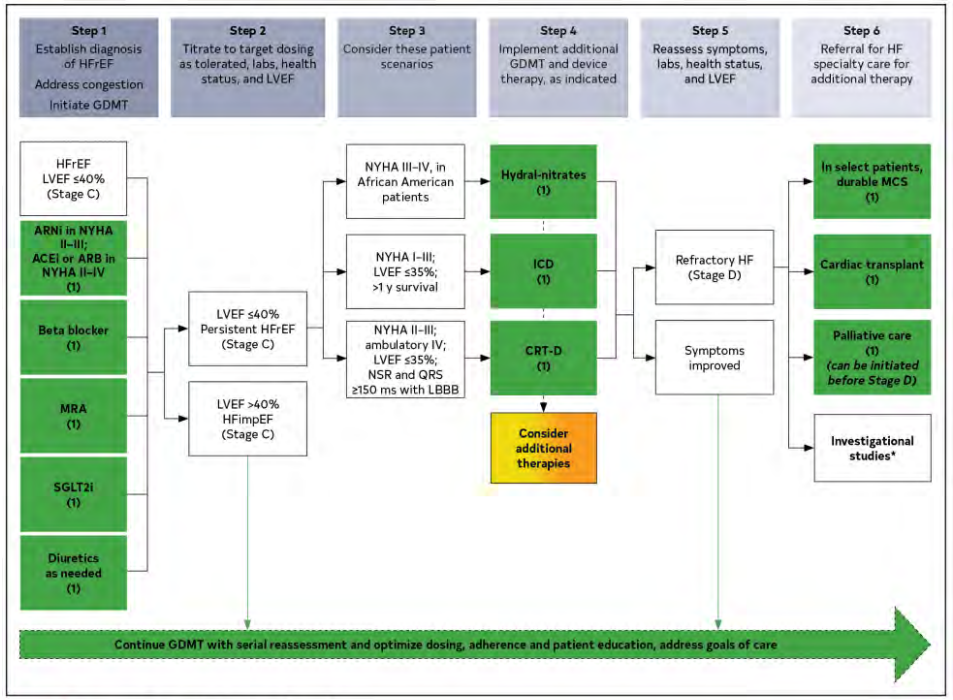


Figure 6. Treatment of HFrEF Stages C and D.

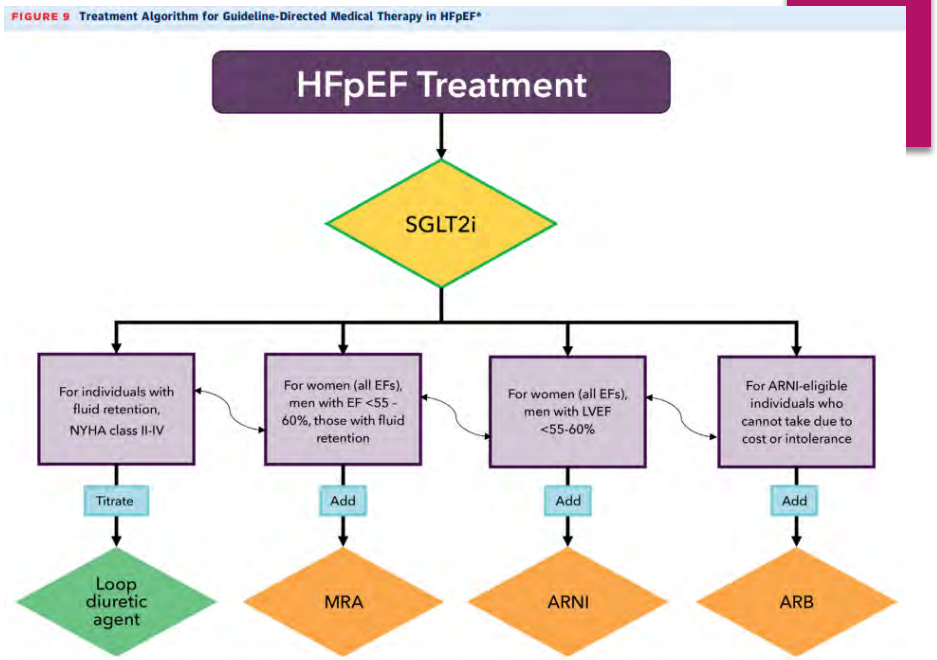


FIGURE 9 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF*

*Green color identifies a Class 1 therapy from clinical practice guidelines,[14] yellow color indicates a Class 2a therapy, and orange color denotes a Class 2b therapy. SGLT2is receive a Class 2a indication in the 2022 AHA/ACC/HFSA HF Guidelines,[14] but the benefit, now confirmed in 2 randomized trials,[60,61] suggests that SGLT2is may

ACC/AHA HF Guidelines

Leqvio (inclisiran)

FDA approval

- Adjunct to diet and statins for primary HLD (including heterozygous famililal hypercholesterolemia) to reduce LDL

Mechanism of action

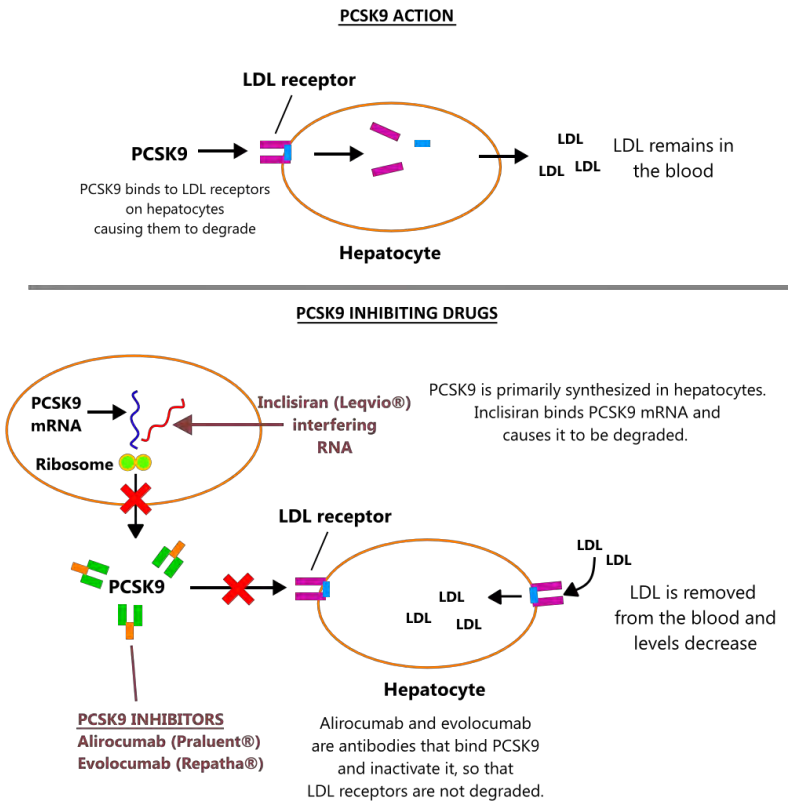
- Small interfering RNA (siRNA) to PCSK9 mRNA

Dosing

- 284 mg SQ at month 0, 3 months, then every 6 months
- Must be done by a health care professional

Side effects (>3%)

- Injection site reaction, arthralgia, and bronchitis



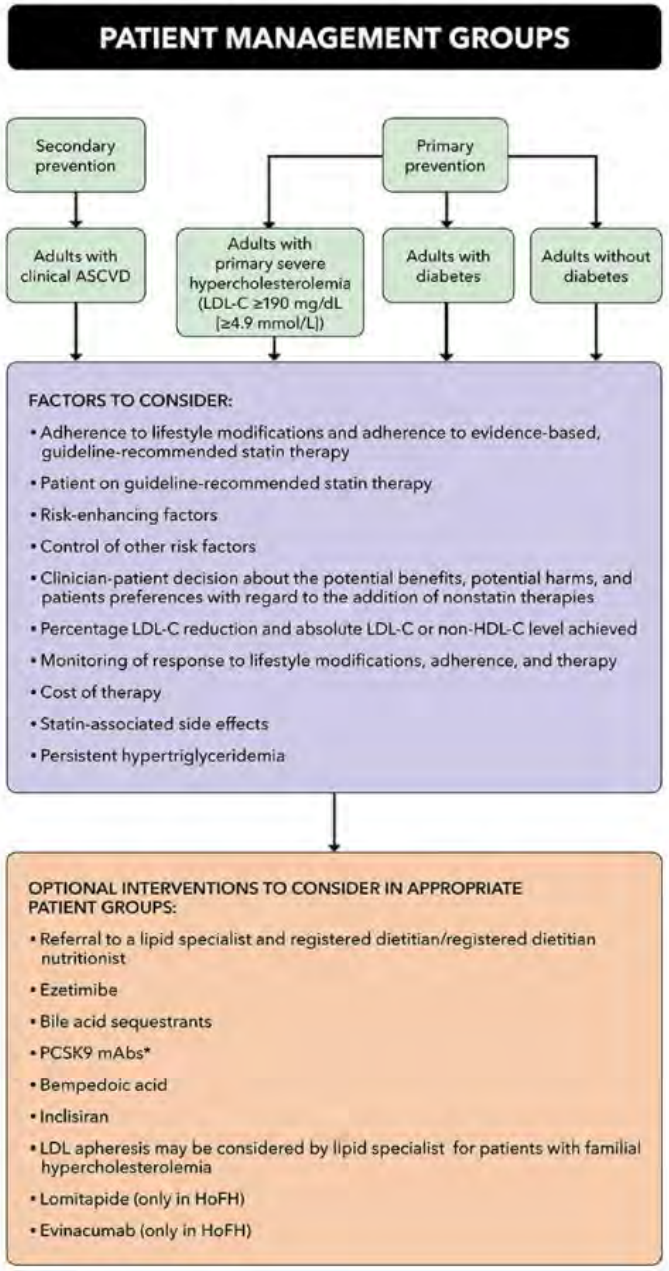
Leqvio (inclisiran)

- Cost: $3500/dose
- Place in therapy
  - Specialist
  - No patient-oriented outcomes yet (like improved CV morbidity/mortality)—other non-statin therapies DO have this data

Inclisiran[43]

- **Mechanism of action:** siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors.
- **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy.
- **Dose:** Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician.
- **Mean % reduction in LDL-C (per PI):** 48%-52%
- **Contraindications (per PI):** None
- **Warnings/precautions (per PI):** None
- **Adverse effects:** Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea
- **Use during pregnancy/lactation:** No safety data in humans; avoid use.
- **Drug-drug interactions (per PI):** None
- **CV outcomes trials:** CV outcomes trials not yet completed. ORION-4 currently in progress with estimated completion in 2026. VICTORION-2P currently in progress with estimated completion in 2027.
- **Other prescribing considerations:** robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization.

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

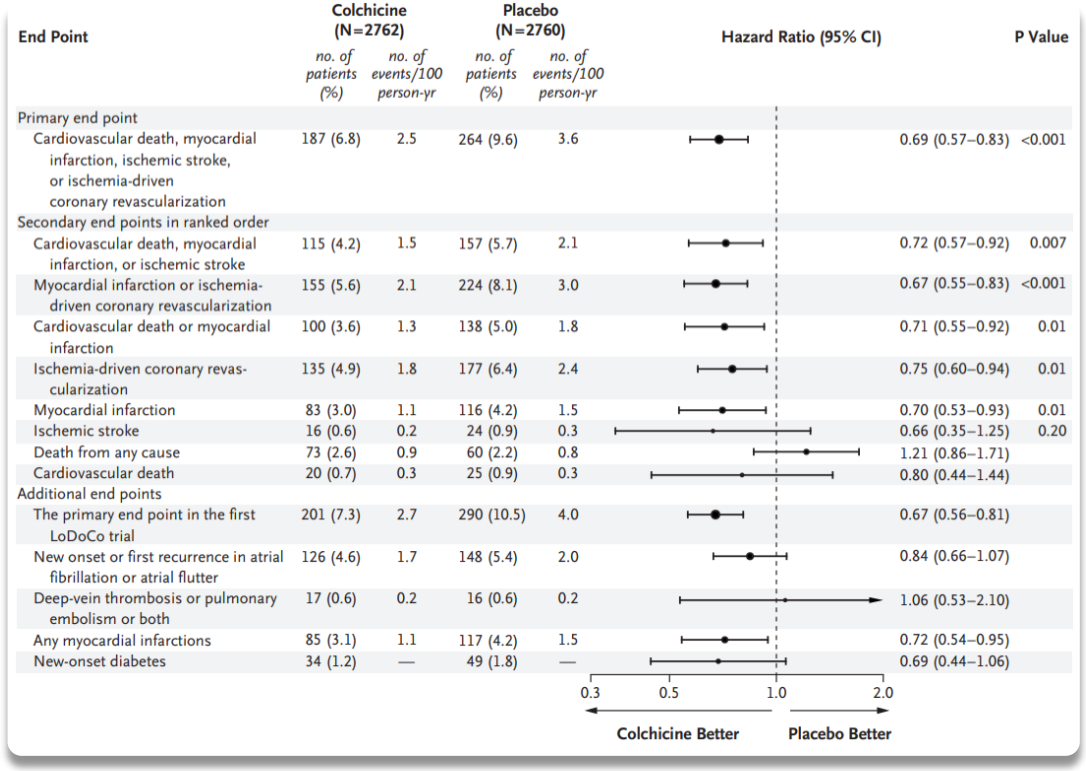


Lodoco (colchicine)

- FDA approval:
  - Reduce risk of stroke, MI, CV death in adults with established ASCVD or multiple risk factors
- Dosing:
  - 0.5 mg daily
- Mechanism of action
  - Thought to be anti-inflammatory (inhibits neutrophils moving to inflammation and decreases their adhesion; decreases CRP)
- Side effects:
  - Diarrhea, nausea, vomiting

LoDoCo (colchicine)

- Supporting evidence:
  - Patients 35-82 with CAD or high coronary artery calcium score (>400 Agatston units)
    - 99.7% on ATP or ATC, 96.6% on lipid-lowering med (~94% on a statin), 62.1% on BB, 71.7% on RAS inhibitor
  - NNT for primary composite endpoint: 35.7
  - 31% RRR
- Cost:
  - ~$530/month
    - "pricing strategy will be focused on helping ensure access to as many people as possible"
- Place in therapy
  - TBD



End Point	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Primary end point						
Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	2.5	264 (9.6)	3.6	0.69 (0.57–0.83)	<0.001
Secondary end points in ranked order						
Cardiovascular death, myocardial infarction, or ischemic stroke	115 (4.2)	1.5	157 (5.7)	2.1	0.72 (0.57–0.92)	0.007
Myocardial infarction or ischemia-driven coronary revascularization	155 (5.6)	2.1	224 (8.1)	3.0	0.67 (0.55–0.83)	<0.001
Cardiovascular death or myocardial infarction	100 (3.6)	1.3	138 (5.0)	1.8	0.71 (0.55–0.92)	0.01
Ischemia-driven coronary revascularization	135 (4.9)	1.8	177 (6.4)	2.4	0.75 (0.60–0.94)	0.01
Myocardial infarction	83 (3.0)	1.1	116 (4.2)	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	16 (0.6)	0.2	24 (0.9)	0.3	0.66 (0.35–1.25)	0.20
Death from any cause	73 (2.6)	0.9	60 (2.2)	0.8	1.21 (0.86–1.71)	
Cardiovascular death	20 (0.7)	0.3	25 (0.9)	0.3	0.80 (0.44–1.44)	
Additional end points						
The primary end point in the first LoDoCo trial	201 (7.3)	2.7	290 (10.5)	4.0	0.67 (0.56–0.81)	
New onset or first recurrence in atrial fibrillation or atrial flutter	126 (4.6)	1.7	148 (5.4)	2.0	0.84 (0.66–1.07)	
Deep-vein thrombosis or pulmonary embolism or both	17 (0.6)	0.2	16 (0.6)	0.2	1.06 (0.53–2.10)	
Any myocardial infarctions	85 (3.1)	1.1	117 (4.2)	1.5	0.72 (0.54–0.95)	
New-onset diabetes	34 (1.2)	—	49 (1.8)	—	0.69 (0.44–1.06)	

Colchicine Fun Facts

- 1st used by ancient Greeks and Egyptians (extracted from autumn crocus)
- Available in US market before 1938
- Unapproved Drug Initiative launched in 2006 to provide the FDA with safety data on older drugs
  - Allowed market exclusivity for manufacturers to take drugs through FDA approval process
- Colchicine went from $0.09/dose → $5/dose

TABLE 3 Average Wholesale Unit Price of Previously Unapproved Prescription Drugs 2 Years Before and After UDI Regulatory Action or Voluntary Approval (N=26) and Unit Price of Specific Manufacturers' Drug Products Immediately Before and After (N=10)[a,b]

	Year of UDI Compliance or Voluntary Approval	Unit Price Before, $	Unit Price After, $	Change in Unit Price, %	Manufacturer Unit Price Before, $	Manufacturer Unit Price After, $	Change in Unit Price, %
Overall, median (IQR)		0.74 (0.23-2.63)	1.24 (0.46-6.20)	37 (23-157)	1.51 (0.57-2.98)	4.05 (1.01-14.40)	122 (10-351)
***P* value**				<0.001			0.013
Drug							
Atropine sulfate ophthalmic solution	2014	3.42	3.88	13.3	2.22	6.35	186.6
Balanced salt solution (ophthalmic)	2008	0.17	0.18	6.1	–	–	–
Codeine phosphate combinations	2014	0.80	1.11	37.8	–	–	–
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			
Colchicine tablet	2010	0.33	5.82	1,663.6	0.17	5.82	3,323.5
Dihydrocodeine bitartrate combinations	2014	2.63	3.36	27.8	–	–	–
Epinephrine injection/syringe	2010	0.49	1.15	136.2	1.44	2.28	58.3
Ergotamine-containing product	2007	107.38	138.60	29.1	1.58	1.89	19.6
Fluorescein injection	2012	6.60	8.94	35.5	–	–	–
Hydrocodone	2007	0.20	0.26	26.2	–	–	–
Hydromorphone injection	2011	1.20	1.34	11.7	1.10	1.01	-8.7
Hydromorphone tablet	2009	0.67	0.85	26.8	–	–	–
Levothyroxine injection	2006	7.20	18.00	150.0	50.93	180.00	253.4
Morphine sulfate immediate-release tablet	2009	0.18	0.20	9.3	–	–	–
Morphine sulfate injection	2011	0.23	0.59	154.3	0.47	0.48	2.1
Morphine sulfate solution	2010	0.08	0.08	4.5	–	–	–
Nitroglycerin sublingual tablet	2010	0.15	0.19	23.3	–	–	–
Oxycodone immediate-release tablet	2009	0.35	0.80	128.6	0.57	0.61	7.0
Oxycodone solution	2010	1.15	5.55	382.6	–	–	–
Pancrelipase	2010	0.46	0.70	51.1	–	–	–
Phenylephrine hydrochloride (IV solution)	2012	2.98	14.40	383.2	2.98	14.40	383.2
Phenylephrine hydrochloride (ophthalmic solution)	2013	1.68	7.50	346.4	–	–	–
Pilocarpine hydrochloride ophthalmic solution	2012	1.94	6.20	220.4	–	–	–
Potassium chloride oral solution	2014	0.02	0.05	222.6	–	–	–
Quinine	2007	3.31	4.06	22.7	–	–	–
Vasopressin	2014	2.18	134.20	6,069.9	5.13	59.40	1,057.9

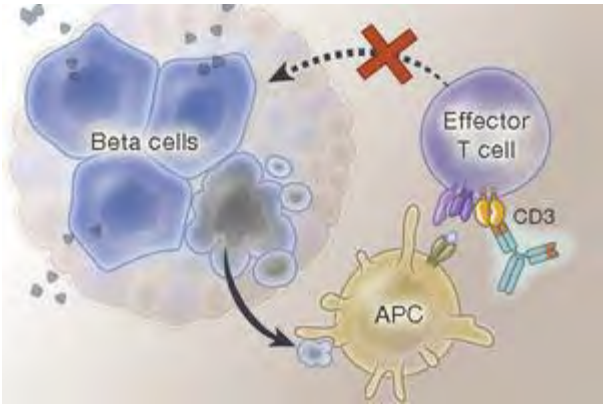
Other Meds

Opill (norgestrel 0.075 mg)

- FDA approval
  - OTC OCP!
    - Kaiser Foundation survey: >3/4 of women of reproductive age favored OTC COP for convenience
- Progestin-only
  - Must be take at the same time every day
  - No missed doses, use back up method if dose is >3 hours late
- Cost
  - Up to $50/month
  - May not be covered by insurance b/c OTC
- Available in pharmacies as of March 2024!

Tzield (teplizumab-mzwv)

- FDA approval
  - Delay onset of T1DM in patients 8 years and older
- Mechanism of action
  - CD3-directed antibody
  - Video https://www.nejm.org/doi/full/10.1056/nejmoa1902226
- Side effects
  - Serious: cytokine release syndrome (CRS), serius infection, lymphopenia, hypersensitivity reactions
    - Can also diminish immunization immune response
  - Less serious: headache, rash



Recommended dosing schedule[1]:

TZIELD is administered by intravenous infusion (over a minimum of 30 minutes), using body surface area-based dosing, once daily for 14 consecutive days.

Day 1	Day 2	Day 3	Day 4	Days 5-14
65 mcg/m^2	125 mcg/m^2	250 mcg/m^2	500 mcg/m^2	1030 mcg/m^2

If a planned infusion is missed, resume course by administering all remaining doses on consecutive days to complete the 14-day course.

Do not administer 2 doses on the same day.[1]

Labs prior to initiation

Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests. Use of TZIELD is not recommended in patients with certain laboratory abnormalities[1]:

- Lymphocyte count less than 1000 lymphocytes/mcL
- Hemoglobin less than 10 g/dL
- Platelet count less than 150,000 platelets/mcL
- Absolute neutrophil count less than 1500 neutrophils/mcL
- Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
- Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
- Active serious infection or chronic active infection other than localized skin infections

Premedication

Premedicate prior to TZIELD infusion for the first 5 days of dosing with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic. Administer additional doses of premedication if needed.[1]

Tzield (teplizumab-mzwv)

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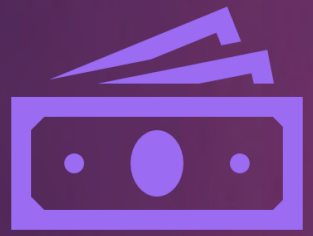

Cost

$194,000 for 14 day course

Place in therapy

Specialist!

Questions?

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