carelon Rx

Today, we are CarelonRx, but when we created this document, we were IngenioRx.

Our name may be new, but our commitment to you remains the same.

Q2 2021

Drug and Biologic Pipeline Update

IngenioRx's quarterly *Drug and Biologic Pipeline Update*

This edition highlights several emerging therapies in the pharmaceutical pipeline and provides an overview of significant Food and Drug Administration (FDA) approvals to expect in 2021. We offer a recap on FDA approvals from 2020 and predict how 2021 may compare. In addition, we examine the potential expansion of use for diabetes medications to cardiovascular indications. We analyze the multiple sclerosis treatment and pipeline landscapes, then examine the opioid epidemic's continuing impact on the pipeline. Finally, we check on the status of interchangeable Humira® biosimilars.

IngenioRx continues to closely monitor the drug and biologic pipeline. We provide this free publication as part of our goals to improve health, reduce waste, lower the total cost of pharmacy and medical care, and estimate future cost impact.

Unless otherwise noted, the information contained in this document was obtained from the Centers for Disease Control and Prevention (cdc.gov), the Food and Drug Administration (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of May 19, 2021.

Top emerging new therapies

We expect these products to have significant impact on health plans and members.

TEPLIZUMAB

Product:
Teplizumab

Indication:
Delay of clinical type 1 diabetes (T1D) in at-risk individuals, as indicated by the presence of two or more T1D-related autoantibodies

Estimated FDA approval:
July 2021

Therapeutic class:
Anti-CD3 monoclonal antibody

Route of administration:
Intravenous (IV) infusion

FDA designations:
Breakthrough; Orphan

Manufacturer:
Provention Bio

Condition:

Type 1 diabetes (T1D) is a disease that causes the immune system to attack and destroy a person's insulin-producing beta cells in the pancreas. The risk of developing T1D is 1 in 300, but if there is a relative with T1D, the risk increases to 1 in 20.[1] T1D usually develops over several years before any clinical signs of disease, such as high blood sugar, are present. Approximately 300,000 people in United States have preclinical T1D.

Role in treatment:

Insulin is the mainstay of treatment for people diagnosed with clinical T1D. There is a strong desire to track preclinical development of, and potentially delay or stop, T1D before it progresses to clinical disease, especially for family members of people with T1D who are at higher risk. People with one or more T1D-related autoantibodies, which are proteins produced by the immune system, have the highest risk of developing clinical T1D.[1] If approved, teplizumab would be the first disease-modifying therapy with potential to delay clinical, insulin-dependent T1D in at-risk people.

Efficacy:

The single pivotal, phase 2, At-Risk trial evaluated people, ages 8 to 45, who did not have diabetes but had a family member diagnosed with T1D. To be enrolled, patients were required to have impaired glucose metabolism and at least two T1D-related autoantibodies. Data are limited, but as of this publication, the time to diagnosis of insulin-dependent T1D was delayed approximately two years for patients given a single 14-day course of teplizumab compared to placebo.

Safety:

Teplizumab caused significantly more patients to develop a skin rash and transient decreases in white blood cells compared to placebo. Overall rates of infection were similar between groups. There is a potential malignancy risk based on the mechanism of action of teplizumab.[2,3]

Financial impact:

The price for teplizumab is unknown, but analysts estimate it to be approximately $24,000 per treatment course. Projected U.S. sales are estimated to be $297M by 2028.[4]

IngenioRx view:

If approved, teplizumab would be the first disease-modifying therapy for T1D. While data are limited to a single, phase 2 study, patients may be receptive to a treatment with potential to delay the development of clinical T1D. Wide acceptance from providers may require additional safety data as cases of transient reactivation of Epstein-Barr virus and cytomegalovirus have occurred with teplizumab treatment.[2] It is unclear if the FDA will request an additional phase 3 study to confirm efficacy and safety for this at-risk preclinical T1D population. Teplizumab is also in late-stage, phase 3 development for newly diagnosed T1D patients, potentially expanding the eligible population in the future.

1 TrialNet. T1D Facts (Accessed January 2021): trialnet.org
2 Herold, K.C., Bundy, B.N., Long, S.A., et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med* 2019; 381:603-613 Published Online June, 9, 2019. DOI: 10.1056/NEJMoa1902226.
3 Sherry, N., Hagopian, W., Ludvigsson, J., et al. *Lancet* 2011; 378: 487–97 Published Online June 28, 2011 DOI:10.1016/S0140- 6736(11)60931-8.
4 Decision Resources Group (Accessed November 2020; registration required): insights.decisionresourcesgroup.com

MARALIXIBAT

Product:
Maralixibat

Indication:
Alagille syndrome (ALGS)

Estimated FDA approval:
October 2021

Therapeutic class:
Bile acid transporter

Route of administration:
Oral

FDA designations:
Orphan, Breakthrough

Manufacturer:
Mirum Pharmaceuticals

Condition:

Alagille syndrome (ALGS) is a rare genetic condition that involves accumulation of excess bile acid in the liver, which can lead to liver damage. It can also affect other parts of the body, including the heart, brain, kidneys, blood vessels, eyes, face, and skeleton. The severity of symptoms varies, and if left untreated, ALGS can lead to severe itching, stunted growth, or liver failure. ALGS affects approximately 1 in 70,000 newborns. About 75% of people diagnosed in childhood live to at least age 20. Certain adults with mild disease can lead normal lives.[5, 6, 7, 8]

Role in treatment:

Maralixibat would be the first FDA-approved therapy for this condition. Current treatment options include symptom control, medications to increase bile flow, and diet management. In severe cases, a liver transplant may be necessary.[5]

Efficacy:

In the ICONIC clinical trial, maralixibat demonstrated significant reductions in bile acids and itching, compared to placebo, over the 18-week treatment period. A four-year extension trial revealed treatment with maralixibat was associated with durability of treatment response. Positive increases in height were also seen.[9]

Safety:

The most frequent treatment-related adverse events seen in clinical trials were diarrhea and abdominal pain.

Financial impact:

Although the product is expected to have a high cost, it is unlikely to have a major impact on overall drug spend due to the rarity of the condition.

IngenioRx view:

Maralixibat would be the first FDA-approved treatment for ALGS. It is also in late-stage development for similar conditions, such as progressive familial intrahepatic cholestasis (PFIC).[10]

5 National Center for Advancing Translational Sciences, Genetic and rare Diseases Information Center. *Alagille syndrome* (Accessed January 2021): rarediseases.info.nih.gov
6 Mirum Pharmaceuticals. Who we are (Accessed January 2021): mirumpharma.com
7 Orphanet. Alagille syndrome (Accessed January 2021): orpha.net
8 News Medical. What is *Alagille Syndrome*? (Updated June 28, 2019): news-medical.net
9 Business Wire. *Mirum Pharmaceuticals Presents Data Demonstrating Long-term Durability of Treatment Effect of Maralixibat in Children With Cholestatic Liver Diseases* (Accessed November 8, 2019): businesswire.com
10 Cision PR Newswire. *Mirum Pharmaceuticals Initiates Phase 3 Clinical Trial for Pediatric Patients with Progressive Familial Intrahepatic Cholestasis* (Accessed July 9, 2019): prnewswire.com

CILTACABTAGENE AUTOLEUCEL

Product:
Ciltacabtagene autoleucel

Indication:
Multiple myeloma

Estimated FDA approval:
November 2021

Therapeutic class:
Chimeric antigen receptor T-cells (CAR-T)

Route of administration:
Intravenous (IV) infusion

FDA designations:
Breakthrough, Orphan

Manufacturer:
Johnson & Johnson

Condition:

Multiple myeloma is a blood cancer that affects a type of white blood cell found in the bone marrow. When these cells are damaged, they spread rapidly and replace normal cells with tumors. Symptoms of multiple myeloma can include bone fracture or pain, low red blood cell counts, tiredness, high calcium levels, kidney problems, or infections. In the U.S. in 2020, it was estimated that 32,270 individuals would be diagnosed and 12,830 would die from multiple myeloma.[11]

Role in treatment:

Ciltacabtagene autoleucel was submitted to the FDA for the treatment of adults with multiple myeloma that is relapsed or not responding to other therapies such as chemotherapy, targeted medications, or radiation.[12] Chimeric antigen receptor T-cells (CAR-T) would be a new approach for the treatment of multiple myeloma in which a patient's T-cells (a type of immune system cell) are taken from the blood and re-engineered to attack cancer cells. They are then infused back into the patient. Ciltacabtagene autoleucel will likely become the second CAR-T therapy to receive FDA approval for multiple myeloma following the recent FDA approval of Abecma™ (idecabtagene vicleucel).

Efficacy:

Ciltacabtagene autoleucel was submitted to the FDA based on data from an ongoing phase 1/2 clinical trial. An overall response rate of 97% was observed with 67% of patients achieving complete response.[13]

Safety:

The most common blood-related adverse events observed in the clinical trial included low white blood cells (96%), low red blood cells (81%), and low platelets (79%). An inflammatory response known as cytokine release syndrome (CRS) was observed in 95% of patients. The majority of these cases were mild with a median duration of four days and 99% of which were resolved within 14 days of onset. The median onset of CRS was at seven days post-infusion, with 89% of patients experiencing CRS onset at day four or later. Neurotoxicity was observed in 21% of patients.[13]

Financial impact:

Analysts predict ciltacabtagene autoleucel will be priced at $377,000 for a one-time treatment, with projected peak U.S. sales of $500M in 2029.[14]

IngenioRx view:

Ciltacabtagene autoleucel may become one of the first FDA-approved CAR-T therapies for the treatment of multiple myeloma. However, the complexities of CAR-T administration limit use of this therapy in the real-world setting. One potential advantage of ciltacabtagene autoleucel is speculation that it could be administered to outpatients due to delay in onset of CRS symptoms. Daily outpatient monitoring may be required for a specific amount of time following infusion, and patients would be admitted for any complications. There are ongoing clinical trials in outpatient use.[15]

11 Janssen initiates rolling submission of a biologics license application to U.S. FDA for BCMA CAR-T therapy ciltacabtagene autoleucel (cilta-cel) for the treatment of relapsed and/or refractory multiple myeloma. (Accessed February 9, 2021): Available at: biospace.com

12 Treating multiple myeloma. (Accessed February 10, 2021): Available at: cancer.org

13 Early, deep, durable responses of ciltacabtagene autoleucel (cilta-cel) observed in Phase 1b/2 CARTITUDE-1 study show potential of BCMA CAR-T in treatment of heavily pretreated patients with multiple myeloma. (Accessed February 10, 2021): Available at: janssen.com

14 Decision Resources Group (Accessed November 2020; registration required): insights.decisionresourcesgroup.com

15 CAR-T a 'fantastic improvement' over available therapies for advanced multiple myeloma. (Accessed February 10, 2021): Available at: healio.com

In addition to the treatments listed previously, there are important drugs and biologics scheduled to receive FDA approval within the next 18 months.

*** Key:**

CGRP: calcitonin gene-related peptide

IL-17: interleukin-17

IM: intramuscular

IV: intravenous

SC: subcutaneous

SGLT2: sodium glucose co-transporter 2

Rolling submission: when a drug company submits completed sections of its application for review instead of waiting until every section of the application is completed; decision date is assigned when the application is complete

Orphan drug/rare disease; expected to be high cost but with minimal impact to overall drug/medical spend due to low utilization

Potential to significantly increase overall drug/medical spend

New entrant into high spend/trending category

No significant impact to incremental spend based on initial analysis

Other significant product approvals

We expect these products to reach the market in 2021/2022.*

Drug or biologic manufacturer	Indication/ route*	Place in therapy*	Estimated approval date	Impact on overall drug spend
Aducanumab Biogen	Alzheimer's disease/IV	**First in class:** first anti-amyloid antibody for treatment of Alzheimer's disease; safety concerns	Accelerated approval on 06/07/2021	
Atogepant AbbVie	Migraine prevention/oral	**Addition to class:** CGRP inhibitor for the prevention of migraine	Third quarter 2021	
Teplizumab Provention Bio	Type 1 diabetes mellitus delay/IV	**First in class:** would be first FDA-approved therapy for delay of diabetes; potential safety issues	07/02/2021	
Avacopan ChemoCentryx	Anti-neutrophil cytoplasmic antibody-associated vasculitis/oral	**Addition to class:** would be first antibody complement 5a receptor inhibitor for this indication; will compete with prednisone	07/07/2021	

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Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route*	Place in therapy*	Estimated approval date	Impact on overall drug spend
Finerenone Bayer	Diabetic nephropathies/oral	**Addition to class:** nonsteroidal mineralocorticoid receptor antagonist; would compete primarily with SGLT2 inhibitors	07/09/2021	
Narsoplimab Omeros Corporation	Hematopoietic stem cell transplant-associated thrombotic microangiopathy/IV	**Addition to class:** would be first FDA-approved treatment for this indication	07/18/2021	
Odevixibat Albireo	Progressive familial intrahepatic cholestasis/oral	**First in class:** would be first FDA-approved treatment for this indication	07/20/2021	
Vosoritide BioMarin	Achondroplasia/SC	**First in class:** would be first FDA-approved treatment for this indication	08/21/2021	

As of May 19, 2021

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route*	Place in therapy*	Estimated approval date	Impact on overall drug spend
Maralixibat Mirum	Alagille syndrome/oral	**First in class:** would be first FDA-approved treatment for this indication	10/01/2021	
Bimekizumab UCB	Plaque psoriasis/SC	**Addition to class:** IL-17 inhibitor will compete with other biologics	10/15/21	
Varenicline Oyster Point	Dry eyes/nasal	**Addition to class:** first intranasal product developed for dry eyes	10/18/2021	
Ciltacabtagene autoleucel Johnson & Johnson	Multiple myeloma/IV	**Addition to class:** will likely be second CAR-T therapy approved for multiple myeloma	2021 (rolling submission)	
Zynteglo®/ LentiGlobin™ (betibeglogene autotemcel) bluebird bio	Beta thalassemia/IV	**First in class:** would be first gene therapy approved for treatment of beta thalassemia; potential safety issues seen in sickle cell disease studies	2021 (rolling submission)	

As of May 19, 2021

Analysis: 2020 FDA approvals year in review

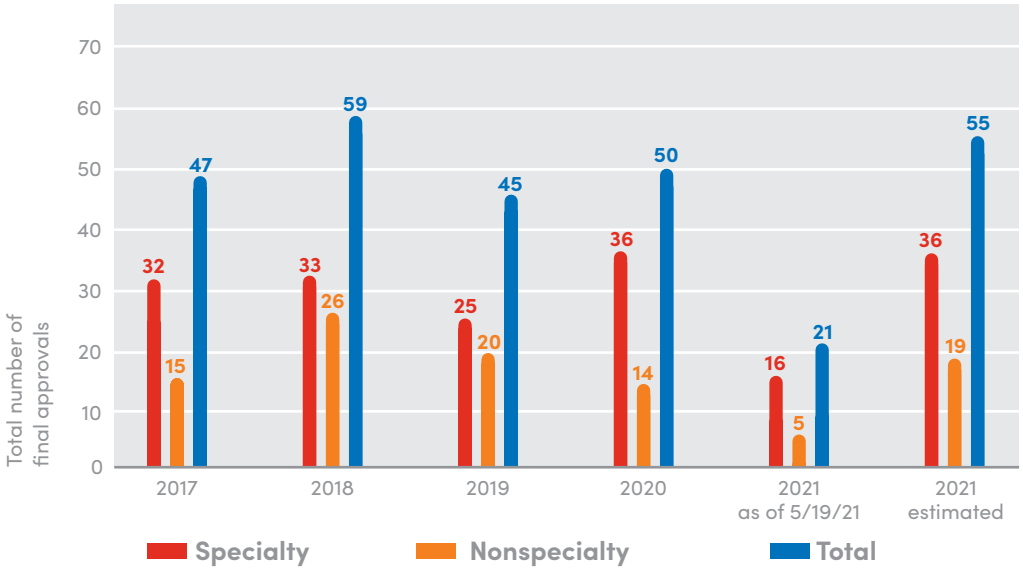
The FDA approved 50 novel drugs or biologics in 2020. Approvals occurred at a rate averaging one per week. One or more expedited pathways were granted for 74% of 2020 approvals.[24]

Other noteworthy statistics[25]

- 64% of approvals were for rare diseases
- 34% of approvals had fast-track status
- 50% of approvals were breakthrough therapies
- 60% of approvals had priority review
- 26% of approvals were accelerated

The above counts may differ slightly from the FDA, depending on how new molecular entity is defined.

FDA approval trends and what to expect in 2021[27, 28]



Total number of final approvals is dependent on FDA reviews and potential denials, delays, or both. As a result, the final 2021 number will likely be lower than shown. Counts may differ slightly from the FDA, depending on how new molecular entity is defined.

24 Regulatory Affairs Professionals Society. *FDA sped progress for most of 2020's novel drugs* (Accessed February 18, 2021): raps.org
25 U.S. Food and Drug Administration. *Novel Drug Approvals for 2020* (Accessed February 18, 2021): fda.gov
26 U.S. Food and Drug Administration. *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review* (Accessed February 23, 2021): fda.gov
27 U.S. Food and Drug Administration. *New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products* (Accessed February 23, 2021): fda.gov
28 FDA Tracker. *Standard FDA calendar* (Accessed February 23, 2021): fdatracker.com

Expedited pathway approval definitions[26]

Fast-track process is designed to expedite the review of drugs or biologics to treat serious conditions and fill an unmet medical need. If there are available therapies, a fast-track drug must show an advantage.

Breakthrough therapy designations are also designed to expedite development and review of drugs or biologics for serious conditions. In this case, preliminary clinical evidence must show substantial improvement over available therapy on a clinically significant endpoint, as defined by the FDA.

Priority review means that the FDA intends to act on an application within six months, compared to 10 months under standard review.

Accelerated approval allows drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint. A confirmatory trial must be completed to ensure continued approval.

Update on multiple sclerosis

What is multiple sclerosis?

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system, including the brain, spinal cord, and optic nerves. The cause of MS is unknown, but it is thought to be a combination of genetic predisposition and exposure to an unknown environmental factor.[29]

When a person has MS, their immune system attacks myelin, a protein that surrounds and protects the nerve cells in the central nervous system. As myelin erodes, it distorts or disrupts the signals traveling through the central nervous system. Which nerves are affected and how badly the myelin is eroded determine a person's symptoms.[29]

Types of MS

There are four main types of MS:[29,30]

- Clinically isolated syndrome (CIS), where a person has had one episode of MS-like symptoms caused by a brain lesion. Not everyone with CIS goes on to develop MS.
- Relapsing-remitting (RRMS), where there are periods of time when symptoms worsen severely, called attacks or relapses, followed by times when symptoms lessen or disappear, called remissions. RRMS is the most common type of MS, comprising about 85% of all initial MS diagnoses.
- Secondary progressive (SPMS), where the disease starts as relapsing-remitting, then begins to steadily worsen within about 10 years. SPMS eventually enters a nonrelapsing, noninflammatory phase.
- Primary progressive (PPMS), where symptoms steadily worsen from the time of diagnosis, without remissions or relapses. About 15% of people with MS have PPMS.

Relapsing MS (RMS) is a term that includes CIS, RRMS, and relapsing SPMS. No one can predict what course a person's MS will take.

Prevalence of MS: A recent study indicates that up to 1 million people in the U.S. are living with MS.[30]

MS treatments: Medications such as disease-modifying therapies (DMTs) that may delay or slow the progression of disease and reduce the number of relapses, are an important part of managing MS. Numerous oral, injectable, and infused DMTs are FDA approved for RMS; in general, guidelines do not recommend one over another.[31] Selection of a DMT is usually individualized, guided by each patient's situation. In addition to RMS, Ocrevus® is the only FDA-approved drug to treat PPMS. There are no FDA-approved treatment options for nonrelapsing SPMS.

MS pipeline: There are several drugs and biologics under investigation for the treatment of MS. The pipeline contains drugs with novel targets, drugs seeking approval for nonrelapsing SPMS, as well as those that work similarly to current FDA-approved therapies. Pipeline drugs in phase 3 or higher are listed in the table on the following page.[32]

29 National Multiple Sclerosis Society. Types of MS (Accessed February 11, 2021): nationalmssociety.org
30 National Multiple Sclerosis Society. How many people live with MS? (Accessed February 11, 2021): nationalmssociety.org
31 Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90:777-88. Available at: https://n.neurology.org/content/90/17/777.long Accessed February 2021.
32 Decision Resources Group (accessed February 2021; registration required): insights.decisionresourcesgroup.com

*** Key:**

BTK: selective bruton tyrosine kinase inhibitors

S1P: sphingosine-1-phosphate

IV: intravenous infusion

TKI: tyrosine kinase inhibitor

SC: subcutaneous injection

Drug or biologic manufacturer	Route/target*	Place in therapy	Estimated approval (phase of development)
Disease-modifying therapies *(DMTs) seeking FDA approval for the treatment of multiple sclerosis (MS)*			
Ublituximab TG Therapeutics	IV/third generation, chimeric, anti-CD20 monoclonal antibody	• Would be the third anti-CD20 monoclonal antibody to treat RMS • Would compete with SC Kesimpta® and IV Ocrevus • Potential dosing advantage with one-hour infusion time compared to Ocrevus' infusion time of 2 hours or longer	2022
Evobrutinib Merck	Oral/selective BTK inhibitor	• Competing to be the first BTK inhibitor in adults with RMS	2024
Fenebrutinib Roche	Oral/selective BTK inhibitor	• Competing to be the first BTK inhibitor in adults with RMS or PPMS • Would compete with Ocrevus for PPMS	Phase 3
Tolebrutinib Sanofi Genzyme	Oral/selective BTK inhibitor	• Competing to be the first BTK inhibitor in adults with RMS, PPMS, or nonrelapsing SPMS • Competing to be the first FDA-approved option for nonrelapsing SPMS • Would compete with Ocrevus for treatment of PPMS	2025 for RMS; 2026 for PPMS and nonrelapsing SPMS
Mastinib AB Science	Oral/tyrosine kinase inhibitor	• Would be the first TKI for MS • Seeking approval for adults with PPMS or nonrelapsing SPMS • Competing to be the first FDA-approved option for nonrelapsing SPMS • Would compete with Ocrevus for treatment of PPMS	Phase 3

The future of MS treatments

With projected approval in 2022, ublituximab may directly compete with other anti-CD20 monoclonal antibodies Ocrevus and Kesimpta® for the treatment of RMS. In trials, an ublituximab infusion is given over one hour compared to the two-hour or longer infusion time required with Ocrevus. Kesimpta can be self-administered by subcutaneous injection. Although Ocrevus has the advantage of being first on the market and having wider FDA-approved indications (RMS and PPMS), the introduction of ublituximab provides additional competition.

Of particular interest are agents in phase 3 development for the treatment of PPMS (mastinib, fenebrutinib, and tolebrutinib) and nonrelapsing SPMS (tolebrutinib and mastinib). Currently, only one DMT, Ocrevus, is FDA approved for the treatment of PPMS. If approved, tolebrutinib may be the first agent FDA approved for nonrelapsing SPMS.

Therapy market trends

Humira biosimilars

Humira® (adalimumab) was approved in 2002 by the FDA to treat rheumatoid arthritis, and with many label expansions, has become the top-selling drug in the United States with $14.8B in U.S. sales in 2019.[33, 34]

Six Humira biosimilars have been approved by the FDA, but none have launched; several more are in late-stage trials. No biosimilars have received interchangeable status (automatically substitutable by a pharmacist). The launch of an interchangeable Humira biosimilar may generate sizable savings. Boehringer Ingelheim is the only company currently pursuing interchangeable status for its Humira biosimilar, Cytelzo, with an anticipated launch in 2023. Data from their interchangeability study started in 2017 is expected to be reported later this year. Launches from other companies would follow during 2023.[35, 36]

Cytelzo is a 50 mg/mL formulation. There is a possibility that citrate-free 100 mg/mL biosimilars could launch as early as August 2022. None of these have yet been approved. This could allow for easier conversion to a biosimilar since the majority of use is for the 100 mg/mL citrate-free Humira product.

Although the active ingredient, adalimumab, is the same in the citrate-free and original Humira formulations, patients have reported less pain immediately following injection with the citrate-free version. If there is not an interchangeable version, hurdles may still exist.[37]

33 AbbVie. Annual report (Accessed February 24, 2021): investors.abbvie.com
34 Axios. The top-selling drugs in the U.S. in 2019 (Accessed February 24, 2021): axios.com
35 Biosimilar Development. Weighing The Potential Of Humira Biosimilars In The U.S. – Competitive Dynamics Analysis (Accessed February 24, 2021): biosimilardevelopment.com
36 Biopharma Dive. With Boehringer settlement, AbbVie completes Humira sweep (Accessed February 24, 2021): biopharmadive.com
37 The Center for Biosimilars. Adalimumab Biosimilars Face Product Obsolescence Before Launch (Accessed February 24, 2021): centerforbiosimlars.com

Update on diabetes

The rapidly expanding diabetes pipeline

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes.[38] Historically, oral diabetes medications were only approved to lower blood sugar (glucose) in adults with type 2 diabetes. Large studies demonstrated that tight control of blood sugar did not prevent cardiovascular (CV) events and may cause harm.[39] In 2007, an analysis of studies suggested that the diabetes medication rosiglitazone may increase the risk of heart attack or CV death in people with type 2 diabetes.[40] Based on these findings, the FDA required manufacturers to demonstrate CV safety for all new diabetes agents by conducting large CV outcomes trials (CVOTs). The goal of these CVOTs was to determine whether new diabetes drugs increased the risk of CV events. Several CVOTs demonstrated CV benefit. This prompted more studies to assess potential benefit of diabetes agents, in addition to blood glucose control.[40]

In 2016, Jardiance® (empagliflozin) became the first diabetes treatment with an FDA-approved indication to reduce the risk of CV death in adults with type 2 diabetes and established CVD, based on results from a large CVOT.

In 2019, Invokana® (canagliflozin) became the first diabetes medication with an FDA-approved indication to reduce the risk of kidney failure, CV death, and hospitalization for heart failure in people with type 2 diabetes and kidney disease. This approval was based on a large study in patients with kidney disease.

In 2020, Farxiga® (dapagliflozin) became the first diabetes medication with an FDA-approved indication for treatment of heart failure in people with or without diabetes based on results from a large CVOT.

38 American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021; 44(Suppl.1): S125–S150. (Accessed February 9, 2021): Available at: care.diabetesjournals.org

39 Brown JM, Everett BM. Cardioprotective diabetes drugs: what cardiologists need to know. Cardiovasc Endocrinol Metab. 2019 Nov 13;8(4):96-105. (Accessed February 26, 2021): Available at: ncbi.nlm.nih.gov

40 Acharya T, Deedwania PC. The Role of Newer Anti-Diabetic Drugs in Cardiovascular Disease. American College of Cardiology. May 23, 2018. (Accessed February 4, 2021): Available at: acc.org

Update on diabetes (continued)

Over the last five years, six drugs from two classes of diabetes medications have gained additional FDA-approved indications:

FDA-approved indications	Sodium glucose co-transporter 2 (SGLT2) inhibitors (oral tablets)			Glucagon-like peptide-1 (GLP-1) agonists (subcutaneous injection)		
	Jardiance (empagliflozin)	Farxiga (dapagliflozin)	Invokana* (canagliflozin)	Victoza® (liraglutide)	Ozempic® (semaglutide)	Trulicity® (dulaglutide)
Type 2 diabetes	✓	✓	✓	✓	✓	✓
To reduce the risk of the following in people with type 2 diabetes and established CV disease:						
CV death	✓					
HHF		✓				
MACE			✓	✓	✓	✓
To reduce the risk of the following in people with type 2 diabetes and diabetic nephropathy with albuminuria:						
ESRD			✓			
Doubling of sCr			✓			
CV death			✓			
HHF			✓			
To reduce the risk of the following in people with heart failure with reduced EF:						
CV death		✓				
HHF		✓				

Key

CV = cardiovascular
EF = ejection fraction
ESRD = end-stage renal disease
HHF = hospitalization for heart failure
MACE = major adverse cardiovascular events
sCr = serum creatinine;
Subcutaneous = applied under the skin

*Invokana can increase the risk for lower limb amputation and bone fracture.

Pipeline for diabetes drugs in cardiovascular and kidney disease indications[41, 42]

Drug	Route	Indication	Estimated approval (phase of development)
		SGLT2 Inhibitors	
Farxiga	Oral	To reduce the risk of CV death or worsening HF in people with heart failure with preserved ejection fraction with or without diabetes	2022
		Prevention of CV death or HHF following a recent myocardial infarction	Phase 3
		Treatment of new or worsening chronic kidney disease (CKD) in individuals with and without type 2 diabetes	Approved 04/30/2021
Jardiance	Oral	To reduce the risk of CV death, HHF, and to slow kidney function decline in adults with chronic heart failure with reduced ejection fraction in individuals with or without diabetes	Between April and May 2021
		To reduce the risk of CV death and HHF in adults with chronic heart failure with preserved ejection fraction in individuals with or without diabetes	Phase 3
		To reduce the risk of kidney disease progression and CV death in adults with CKD in individuals with and without type 2 diabetes	Phase 3
Invokana	Oral	Heart failure in individuals with or without diabetes	Phase 3
		GLP-1 Agonists	
Ozempic	Subcutaneous injection	Diabetic nephropathy	Phase 3
		SGLT1/SGLT2 Inhibitor	
Zynquista	Oral	Heart failure in individuals with diabetes	2022

The future of diabetes treatments: There is huge potential for newer diabetes agents to improve health and reduce hospitalizations in people with diabetes, as well as those who do not have the disease. Differing safety profiles and routes of administration will help guide therapy selection. In the near future, these medications may no longer be used mainly for diabetes, as they are becoming options for non-diabetic people with chronic kidney disease or heart failure.[43, 44]

41 AstraZeneca 2020 earnings release. (Accessed February 19, 2021): Available at: astrazeneca.com
42 AHA 2020 – sotagliflozin wins come too late for Lexicon. (Accessed February 19, 2021): Available at: evaluate.com
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The opioid epidemic

Widespread misuse of opioids led the U.S. Department of Health and Human Services to declare a public health emergency in 2017. Approximately 10.3 million people misused prescription opioids, and 46,802 deaths were attributed to all opioids in 2018.[45] The estimated total economic burden of the opioid crisis in the U.S. from 2015 to 2018 was at least $631 billion.[46]

Drug overdose deaths have accelerated during COVID-19, with over 81,000 reported in the 12 months ending in May 2020, the highest number ever recorded in a 12-month period. Illegally manufactured fentanyl appears to be the primary cause of the increases in overdose deaths.

Treatment options

Opioid use disorder management consists of withdrawal, maintenance, and emergency overdose treatment. Medically supervised withdrawal may be completed with methadone or buprenorphine and symptomatic therapies. Medication-assisted treatment (MAT) for maintenance therapy includes methadone, buprenorphine products, and naltrexone extended release (XR).

Emergency treatment of opioid overdose starts with nasal or injectable naloxone followed by immediate emergency medical assistance. Many states allow pharmacy dispensing of naloxone without a prescription to increase availability and reduce deaths.[47] Naloxone may be available over the counter (OTC) in the future.[48]

Decreasing opioid prescribing and overdose deaths

In 2016, the Centers for Disease Control and Prevention (CDC) issued guidelines for prescribing opioids for chronic pain. The overall intent was to improve communication between prescribers and patients, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy. In 2015, policy changes resulted in a 60% reduction in the number of opioid prescriptions filled. The implemented policies helped reduce opioid prescribing and prevent or deter opioid use disorder, along with improving treatment and recovery.[49]

Future of opioid use disorder management

The pipeline for opioid use disorder treatments is highlighted by higher-dose naloxone products and opioid antagonists with longer duration of action, such as nalmefene.[50, 51] There is also interest in additional abuse-deterrent opioids and nonopioid pain relievers, including nerve growth factor inhibitors.[52]

Opioid prescriptions will continue to decline in favor of nonopioid alternatives. The class is projected to grow in major markets by only 4.4%, from approximately $4.5 billion in 2018 to $5.5 billion in 2028.[53]

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