KASTURBA MEDICAL COLLEGE
MANIPAL
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THE DRUG TIMES

Newsletter from Department of Pharmacology, Kasturba Medical College, Manipal
Issue 10, December 2023

The current issue of THE DRUG TIMES provides information about RNA therapeutics, a breakthrough in managing anemia due to CKD, neuroactive steroids use in PPD, a new malaria vaccine, a gamechanger in the treatment of HIV, Oxygen cocktail, a report on National Pharmacovigilance week celebration 2023, discovery of Streptomycin and FDA new drug approvals.

THE EMERGING TRENDS OF RNA THERAPEUTICS

In the last two-three decades, there has been a significant emphasis on exploring the potential of RNA in the treatment of cancers, genetic diseases, neurodegenerative disorders, infectious diseases, etc.

In October 2023, Katalin Karikó and Drew Weissman were awarded the Nobel prize in Physiology or Medicine for their discoveries that helped in the development of mRNA vaccines against COVID-19 virus.

4 main types of RNA therapeutics have been identified based on their mode of action & structural characteristics (majority of the drugs belong to first two categories). They are as follows –

1. **Anti-sense oligonucleotides (ASOs)**
   ASOs are short, single-stranded, non-coding RNA (or DNA) that have base pairs complementary to a certain region of mRNA or pre-mRNA which they are meant to target, thereby disrupting their expression & inhibiting protein synthesis.
2. **Small interfering RNA (siRNA)**
   In contrast to ASOs, siRNAs are short, double-stranded, non-coding RNAs which use the endogenous RNA Interference (RNAi) pathway (a natural defence mechanism against RNA viruses) to modulate the expression of target mRNA.
3. **RNA Aptamers**
   Aptamers are short, single-stranded, non-coding RNA (or DNA) that selectively bind to and modulate variety of targets like proteins, whole cells & viruses by virtue of their 3-D structure.
4. **Messenger RNA (mRNA)**
   Exogenously administered mRNAs get translated into proteins which induce an immune response

in the body against infectious diseases & cancers (Personalized Immunotherapy). RNA-based vaccines have garnered a lot of attention in the past 3 years due to the COVID-19 pandemic. The relatively short development time, high in-vitro transcriptional response, availability of efficacy and safety data on therapeutic application of mRNA lead to the rapid approval of two novel COVID-19 vaccines; Tozinameran & Elasomeran, by the US FDA for emergency use, while many others are currently in the pipeline. India's 1st indigenous COVID-19 mRNA vaccine GEMCOVAC-19 (HGC019) was approved by the DCGI in 2022, followed by the approval of GEMCOVAC-OM (mRNA vaccine against the Omicron strain) a year later. mRNA vaccines are also being studied for other infections like Influenza, rabies, RSV, CMV etc. In addition, individualised mRNA vaccines and immunomodulators targeting specific tumors like melanoma, prostate, lung, breast, head and neck, ovarian cancers etc. are in the pipeline as well.

RNA drug	***Year of Approval***	***Mechanism of action***	***Target disease***	***Route***
1. ASOs				
Fomivirsen (withdrawn)	*1998*	*Inhibits expression of viral mRNA coding IE2 protein*	*CMV retinitis*	*Intravitreal*
Mipomersen	*2013*	*Induces RNAse-mediated degradation of Apolipoprotein mRNA*	*Familial hypercholesterol-emia*	*Subcutaneous*
Some recently approved ASO drugs are Nusinersen (2016) for Spinal muscular atrophy, Eteplirsen (2016), Golodirsen (2019) & Viltolarsen (2020) for Duchenne muscular dystrophy.				
2. siRNA				
Patisiran	*2018*	*RNAi-mediated cleavage of transthyretin mRNA*	*Hereditary transthyretin amyloidosis*	*Intravenous*
Givosiran	*2019*	*RNAi-mediated cleavage of ALA synthase 1 mRNA*	*Acute hepatic porphyria*	*Subcutaneous*
Some recently approved siRNA drugs are Lumasiran (2020) & Nedosiran (2023) for primary hyperoxaluria and Inclisiran (2021) for primary hypercholesterolemia.				
3. RNA Aptamers				
Pegaptanib (only RNA aptamer drug to be approved as of today)	*2004*	*Binds to, and blocks the function of Vascular endothelial growth factor*	*Age-related macular degeneration*	*Intravitreal*
4. mRNAs *(Vaccines)*				
Tozinameran (Pfizer-BioNTech)	*2020 (EUA*)*	*Both induce immune response to SARS-COV-2 spike protein antigen*	*COVID-19*	*Intramuscular*
Elasomeran (Moderna)	*2021 (EUA*)*			

**EUA = Emergency Use Authorization*

RNA-based drugs can target ‘undruggable’ molecules which is not seen with traditional small molecule drugs. Other advantages are ease of production (a factor that helped in the quick development of COVID-19 vaccines), cost-effective development and long-term effects with very low risk of genotoxicity. Along with these factors, the availability of drug delivery systems has made RNA therapy an attractive treatment option. And with the 2020 pandemic bringing significant spotlight on it, this field is expected to advance rapidly in the coming days.

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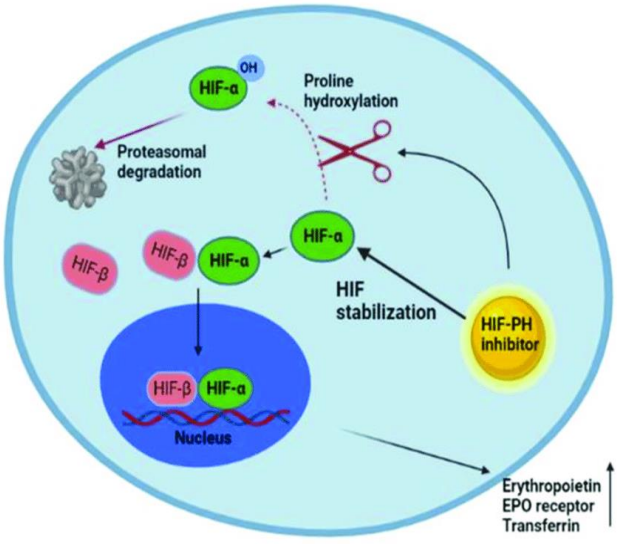
1. Kim YK. RNA therapy: rich history, various applications, and unlimited future prospects. Experimental & Molecular Medicine. 2022 Apr;54(4):455-65.
2. Damase TR, Sukhovershin R, Boada C, Taraballi F, Pettigrew RI, Cooke JP. The limitless future of RNA therapeutics. Frontiers in bioengineering and biotechnology. 2021:161.
3. Duan Q, Hu T, Zhu Q, Jin X, Chi F, Chen X. How far are the new wave of mRNA drugs from us? mRNA product current perspective and future development. Frontiers in Immunology. 2022 Sep 12;13:974433.

A BREAKTHROUGH IN MANAGING ANEMIA DUE TO CKD

Daprodustat is the sole approved therapy given orally for treating anaemia due to chronic kidney disease (CKD) in individuals dependent on dialysis.

It is an enzyme inhibitor of HIF-prolyl hydroxylase that is reversible. By this mechanism, the drug increases the concentration of HIF-α, which in turn boosts the production of HIF-responsive genes like erythropoietin. This ultimately encourages higher levels of red blood cell formation and increases haemoglobin concentrations in patients with end-stage renal failure.



Clinical trials have proven its safety and efficacy, demonstrating that it is not inferior to darbepoetin and indicating a possible reduction in the need for IV iron. In phase 3 trials, daprodustat therapy enhanced total iron binding capacity and decreased serum ferritin, transferrin saturation, and hepcidin levels in non-dialysis patients and peritoneal dialysis, hemodialysis patients.

The lowest dose of Daprodustat that is sufficient to minimise the need for red blood cell transfusions is advised, as it raises the risk of thrombotic vascular events, including significant adverse cardiovascular events.

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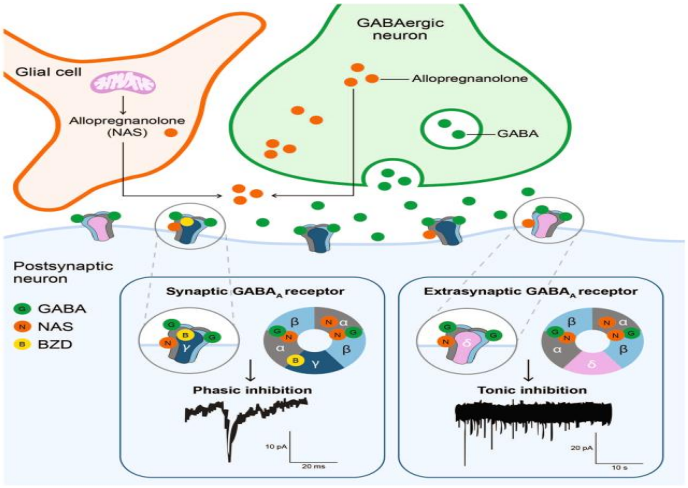
Crugliano G, Serra R, Ielapi N, Battaglia, Y, Coppolino G, Bolignano D, Bracale UM, Pisani A, Faga T, Michael A *et al*. Hypoxia-Inducible Factor Stabilizers in End Stage Kidney Disease: "Can the Promise Be Kept?" Int. J. Mol. Sci. 2021, 22, 12590. doi: 10.3390/ijms222212590.

NEUROACTIVE STEROIDS: EMERGING THERAPY IN THE MANAGEMENT OF POST-PARTUM DEPRESSION (PPD)

To control neuronal excitability, neuroactive steroids (allopregnanolone), which are positive allosteric modulators (PAMs) of GABAA receptors, target the ion channels and neuronal membrane receptors of GABAA receptors. The activity of neuroactive steroids (NASs) at neuronal GABAA receptors occurs in minutes, in contrast to the extended duration and delayed onset of action for steroid hormones. They alter the equilibrium between excitatory and inhibitory pathways and homeostatic processes, which govern mood, aggression, memory, mood, and pain.

Postpartum depression affects 10-15% of new mothers globally. Postpartum depression (PPD) is thought to arise as a result of the inability to upregulate GABAA receptors in response to the rapid decline in allopregnanolone levels during the postpartum period.

In 2019, the FDA approved the use of brexanolone, a NAS GABAA receptor positive allosteric modulator (PAM) that is chemically identical to endogenous allopregnanolone, to treat PPD in adults. Brexanolone's 60-hour continuous infusion period may limit its use. In August 2023, the US FDA approved the oral synthetic NAS and PAM of synaptic and extrasynaptic GABAA receptors, called zuranolone, for the treatment of postpartum depression. It is effective in PPD when administered for 2 weeks at a dose of 50 mg either alone or as adjunct to other antidepressant therapy. It has a favorable safety profile with mild CNS depressant effects such as somnolence and dizziness. Zuranolone may find prospects in major depression as well in the future.



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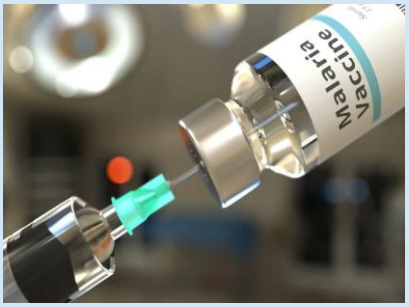
R21/MATRIX-M: A NEW MALARIA VACCINE



Malaria is still a major public health issue in India. In Asia, 83% of malaria cases was stated to be in India, according to the World Health Organization (WHO) 2021 report. A new vaccine, R21/Matrix-M has been recommended by the World Health Organization (WHO) to prevent malaria in children. Supported by the WHO Director-General, the recommendation is in line with recommendations from the Malaria Policy Advisory Group (MPAG) and the Strategic Advisory Group of Experts on Immunization (SAGE). R21 vaccine is developed against *P.falciparum* and targets pre-erythrocytic"sporozoite" the first form that enters the human body after mosquito bite and generates high immunogenicity, both humoral and cellular immunity.

Clinical safety and efficacy of vaccine was proved by clinical study. The vaccine , administered at a dosage of 10 micrograms injected intramuscularly (IM) four weeks apart prior to the seasonal peak,was effective. A booster dose was administered to all individuals, aged 5-17 months, 12 months following their third

dose. In highly seasonal malaria transmission locations, efficacy was shown to be 75% after a 3-dose series over a 12-month period, which meets the long-standing WHO aim of vaccine development to achieve a goal of 75% efficacy against malaria by 2030.The study also discovered that the vaccine was safer, and in most of cases the local and systemic adverse events were of mild grade and no reported serious adverse events.

An important advantage of this vaccine is that it can be manufactured in large scale and it is economical at a cost of 2-4 USD per dose apart from good safety and efficacy. The R21 malaria vaccine is expected to be rolled out by mid-2024 and phase 3 clinical trial results are awaited.(3)

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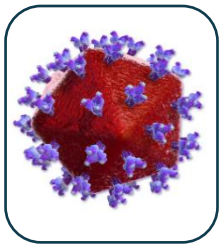
1. Summary of World Malaria Report 2021. 2021. https://www.who.int/india/health-topics/malaria/summary-of-world-malaria-report-2021.
2. https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization.
3. Datoo MS, Natama MH, Somé A, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet. 2021;397(10287):1809-1818. doi:10.1016/S0140-6.

THE GAMECHANGER IN THE TREATMENT OF HIV



HIV (Human Immunodeficiency Virus) is a retrovirus infection affecting the immune system and eventually progressing to AIDS (Acquired Immunodeficiency Syndrome). According to WHO, as of 2022, an estimated 39 million people worldwide are living with HIV. The first drug effective in the treatment of HIV was a nucleoside reverse transcriptase inhibitor named zidovudine, approved by FDA in 1987. Several other NRTIs in combination trailed in HIV treatment and became representatives of early antiretroviral therapy (ART). In 1996 the concept of three-drug therapy (combination of 2 NRTI and a protease inhibitor) gave birth to a new regimen called HAART (highly active antiretroviral therapy) showing an 80% decline in rates of AIDS, death, and hospitalization which was only 60% with ART.

Cabotegravir and rilpivirine extended-release injectable suspension (Cabenuva) is the first FDA-approved injectable launched in 2021 and was preceded by two randomized clinical trials (FLAIR and ATLAS) conducted at multiple sites in different countries including the United States. In these trials, 1,182 HIV-infected adults were virologically suppressed (HIV-1 RNA less than 50 copies/ml) before initiation of treatment and continued to be the same with no clinically relevant change from

baseline in CD4+ cell counts thereby establishing the safety and efficacy of the combination. FDA also approved cabotegravir tablets (VOCABRIA) to be taken in combination with oral rilpivirine (EDURANT) for a month before starting Cabenuva to ensure the medications are well-tolerated before switching to the extended-release injectable formulation.

Cabotegravir is an integrase strand transfer inhibitor (INSTI) whereas rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Currently, this combination is indicated as a complete regimen for virologically suppressed patients on a stable antiretroviral regimen with no history of treatment failure. The recommended oral lead-in daily dose is one 30-mg tablet of cabotegravir and one 25-mg tablet of rilpivirine to be taken for a month followed by the injection on the last day of oral lead-in. Recommendations have also been made if the patient misses the scheduled dose anywhere from 7 days to more than 2 months since the last injection. This combination is contraindicated in patients who are on enzyme inducers like phenytoin, carbamazepine, rifampin, dexamethasone as they will reduce the efficacy of the drugs. Besides injection site reactions like pain and swelling, adverse effects like fever, musculoskeletal pain, vasovagal symptoms, hepatotoxicity, and depression have been reported.

https://www.fda.gov/drugs/human-immunodeficiency-virus-hiv/fda-approves-cabenuva-and-vocabria-treatment-hiv-1-infection

OXYGEN COCKTAIL: FOAM OF THE FUTURE?

An oxygen cocktail is a solution, lightly frothed and infused with high levels of oxygen. The theory behind oxygen cocktails is to provide the body with an additional source of oxygen, which is believed to have several health advantages. Water, milk, syrups, fruit drinks, and juices (grape, cherry, raspberry, etc.) are frequently used as the cocktail's foundation. Plant and herb extracts like mint, thyme, motherwort, hawthorn, strawflower, and rose hip, may be present in the base liquid.

An indispensable component of the oxygen cocktail is the frothing ingredient, which could be liquorice or gelatinous egg white. Cocktail preparation requires combining the above ingredients, adding a frother, and allowing the mixture to foam and get saturated with oxygen.

An oxygen cocktail promotes digestion and causes the breakdown of nutrients by activating the gastrointestinal tract's motor, enzymatic, and secretory processes as well as restoring normal intestinal microbiota. Over the long run, it improves immunity, reduces oxidative stress, and allay fatigue by improving oxygenation. It enhances hemoglobin content and optimizes sugar concentration in blood. It also enhances the function of the neurological, respiratory, and cardiovascular systems. By preventing hypoxia it helps the fetus develop optimally during pregnancy.

The various conditions where the oxygen cocktail is currently being tried are

1. Patients with coronary heart disease
2. Chronic asthma and COPD patients
3. Diabetic and obese patients
4. Sportsmen to improve performance
5. In patients with functional disorders, insomnia and chronic fatigue
6. Expecting mothers
7. Protection against smog and air pollution

Contraindications

1. Intolerance to one or more contents of the oxygen cocktail
2. Gastritis, ulcers, and adhesions of GIT
3. Acute exacerbation of bronchial asthma, respiratory insufficiency
4. Hyperthermia
5. Stones in the urinary bladder and gall bladder

In Russia, it is famous as it provides a rapid energy boost, and most information on oxygen cocktail are obtained from their experience. Very few studies to date have been conducted in a controlled manner to prove these effects. Oxygen is essential for breathing and the human body controls the amount of oxygen available in inspired air. Excessively high oxygen intake or attempting to gain oxygen by non-traditional methods, such as oxygen cocktails, may not always be beneficial to health and may even be harmful. More evidence needs to be generated scientifically to prove their benefits and safety.

References:

1. *https://patents.google.com/patent/RU2150856C1/en*
2. *https://www.nadzeya.by/en/services/procedures/oxygen-cocktails-with-dietary-supplements-medicinal-herbs/*

NATIONAL PHARMACOVIGILANCE WEEK CELEBRATION 2023

From September 17–23, 2023, Adverse Drug Reaction Monitoring Centre, Department of Pharmacology, KMC, Manipal had its third National Pharmacovigilance Week Celebration (NPW).

Posters commemorating National Pharmacovigilance Week were put up in the clinical departments and pharmacies of Kasturba Hospital, Manipal. The centre conducted various activities concerning awareness programs for the public and sensitization for the students.

An e-poster presentation competition on "Public participation in Pharmacovigilance" was held among students from medical, nursing, pharmacy, and health professions colleges under the Manipal Academy of Higher Education to promote active participation among students.

Faculty and post-graduates from the pharmacology department conducted awareness training for patients at the Departments of Medicine and Dermatology regarding reporting adverse drug reactions. The purpose of the session was to promote patient safety. The patient/caretaker's education and awareness session was also conducted near the hospital pharmacy, Kasturba Hospital, Manipal. A pharmacovigilance awareness program and sensitization on reporting ADRs for school students of Class 11 and 12 was conducted by the faculty of the pharmacology department with a total participation of 350 students.

The spread of Pharmacovigilance Awareness Week (NPW) was done on the social media website of Kasturba Medical College, Manipal. The AMC also participated in the national level competition conducted by PvPI on the theme "Boosting Public Confidence in Pharmacovigilance". On September 23, 2023, a valedictory celebration was held to celebrate the successful conclusion of the third NPW 2023. Faculty members, participants, and prize winners were in attendance.

SOIL YIELDS A BOUNTY: THE SAGA OF STREPTOMYCIN

Selman Abraham Waksman was a Russian who relocated to the United States and earned a Ph. D in Biochemistry. He always reminisced about the earthy scent of his native soil and attributed it to actinomycetes, a group of harmless fungus-like bacteria. In pursuit of its practical applications, Waksman received a grant from the pharmaceutical company Merck to conduct research into antibiotics, due to the prevalent general lack of interest post-penicillin success. Following the lead of tyrothricin, a crystalline antibiotic from a soil organism discovered by a Frenchman Rene Dubos, Waksman dedicated the next four years to isolating thousands of different microbes from soil, and methodically screening them for their bactericidal effect. In 1942, following an intensive study of ten micro-organisms, Waksman isolated two different antibiotics: Actinomycin and Streptothricin, which were not fit for clinical use owing to their toxicity. Among Waksman's postgraduates was a remarkably brilliant student called Albert Schatz. He analysed various soil samples over more than 100 days and one among them grew greenish-grey colonies. Because these actinomycetes were green in colour, they were named Streptomyces griseus. Surprisingly, almost three decades earlier, this same organism had been discovered by Waksman. Tests quickly showed that the organism was active against staphylococci and had good bactericidal effect on the gram-negative bacteria previously unaffected by penicillin.

Having served in the army, Schatz had seen the devastation caused by tuberculosis, known as consumption, then, whose only treatment was prolonged rest and nutritious food. He therefore decided to move on to the next phase of research to find an antibiotic that would treat tuberculosis. He demonstrated that streptomycin was remarkably successful in preventing the growth of tubercle bacilli in his tests against tuberculosis. Following this discovery, Waksman won the highly admired Albert Lasker Award, often considered a precursor of the Nobel Prize in Medicine. Even though Schatz had really done the discovery, Waksman set up a business to capitalize on it. Schatz brought a lawsuit seeking payment for royalties and official acknowledgment as a co-discoverer of streptomycin. This case was highly publicized as it pitted a former PhD candidate against a globally renowned professor.

Two years following the settlement, in 1952, Waksman was the only one to win the Nobel Prize in Medicine. Schatz attempted in vain to win a portion of the Nobel Prize. However, Waksman's discovery was overshadowed in the very same year by the development of isoniazid, a drug that could be given orally and was a far more potent cure for tuberculosis. Though streptomycin had a tumultuous journey, it paved the way for future aminoglycoside antibiotics which till date remain one of the best drugs to treat gram-negative infection.

Reference: Meyers, M. A. (2007). Happy accidents: serendipity in modern medical breakthroughs. New York: Arcade Pub.

FDA NEW DRUG APPROVALS

(Aug2023 – Dec2023)

Sl No.	*FDA Approved Drugs*	*Mechanism of action / Class of drug*	*Indication*
1	Zuranolone	Neuroactive steroid GABA- A receptor-positive modulator	Postpartum depression
2	Avacincaptad pegol	Complement inhibitor	Age-related macular degeneration
3	Talquetamab-tgvs	GPRC5D-directed CD3 T-cell engager	Multiple myeloma
4	Elranatamab-bcmm	B cell maturation antigen (BCMA)-directed CD3 T-cell engage	
5	Palovarotene	Retinoid	Fibrodysplasia ossificans progressiva
6	Pozelimab-bbfg	Complement inhibitor	Protein-losing enteropathy (PLE), known as CHAPLE disease
7	Motixafortide	Hematopoietic stem cell mobilizer	Autologous transplantation in multiple myeloma patients
8	Momelitinib	Kinase inhibitor	Intermediate or high-risk myelofibrosis
9	Gepirone	5HT1A agonist	Major depressive disorder
10	Cipaglucosidase alfa-atga	Hydrolytic lysosomal glycogen-specific enzyme	Late-onset Pompe disease
11	Nedosiran	LDHA-directed small interfering RNA	Primary hyperoxaluria type 1
12	Etrasimod	Sphingosine 1-phosphate receptor modulator	Active ulcerative colitis in adults
13	Mirikizumab-mrkz	Interleukin-23 antagonist	
14	Zilucoplan	Complement inhibitor	Generalized myasthenia gravis
15	Bimekizumab	Humanized interleukin-17A and F antagonist i	Moderate to severe plaque psoriasis

16	Vamorolone	Corticosteroid	Duchenne muscular dystrophy
17	Toripalimab-tpzi	Programmed death receptor-1 (PD-1)	Recurrent or metastatic nasopharyngeal carcinoma
18	Fruquintinib	Kinase inhibitor	Refractory, metastatic colorectal cancer
19	Taurolidine, heparin	Combination of taurolidine, a thiadiazinane antimicrobial, and heparin, an anti-coagulant	Catheter-related bloodstream infections in hemodialysis patients
20	Repotrectinib	Kinase inhibitor	ROS1-positive non-small cell lung cancer
21	Efbemalenograstim alfa-vuxw	Leukocyte growth factor	Neutropenia
22	Capivasertib	Kinase inhibitor	Breast cancer
23	Nirogacestat	Gamma secretase inhibitor	Progressing desmoid tumors
24	Iptacopan	Complement factor B inhibitor	Paroxysmal nocturnal hemoglobinuria

Reference

fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023

"The greatest medicine of all is teaching people how not to need it"

- Hippocrates

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