Twelfth Issue
Jan-Mar
2023

PHARMACOALERT

NEWSLETTER

Contents:

PUBLISHED BY
DEPARTMENT OF PHARMACOLOGY
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LUCKNOW

From The Desk of Editorial Team

Greetings!!!

The Department of Pharmacology, Dr. RMLIMS, Lucknow, is pleased to present the twelfth issue of our newsletter 'PHARMCOALERT'. In this issue we have compiled various recent articles of interest like New Drug approved Zavegepant Nasal Spray, Drug Safety Alerts (Jan-Mar 2023), Biotechnology:A novel tool of drug development etc.

The NCC at IPC, Ghaziabad under the PvPI released the letter revealing the actions taken by CDSCO as outcome of PvPI which was communicated to all states/UT regulatory authorities and manufacturers by CDSCO for taking appropriate regulatory actions. It contains the recommendation of signal review panel on different suspected drugs from December 2014 to November 2022.

We thank Department of Radiodiagnosis, Dr.RMLIMS, Lucknow for reporting maximum number of ADRs during Jan-Mar 2023.

In the newer drugs approved section, information about new drugs approved by US-FDA between Jan-Mar 2023 has been mentioned. "Zavegepant Nasal Spray" approved by FDA in March 2023 for 'acute treatment of migraine with or without aura in adults' has been discussed in detail in this issue.

Further to update, "Biotechnology: A novel tool of drug development" has been included in this issue. Biotechnology has significantly influenced the process of discovering and developing new drugs and has significantly enhanced human health and wellbeing It took place as a result of improved understanding of the diseased signalling pathways that made it possible to identify the prospective therapeutic targets.

Hope you all enjoy reading this compilation.

Outcome of Pharmacovigilance Programme of India (PvPI)

The NCC at IPC, Ghaziabad under the PvPI released the letter revealing the actions taken by CDSCO as outcome of PvPI which was communicated to all states/UT regulatory authorities and manufacturers for taking appropriate regulatory actions. It contains the recommendation of signal review panel on different suspected drugs from December 2014 to November 2022 which include actions like drug safety signals, changes in Prescribing Information Leaflet/Patient Information Leaflet (PIL) and drug safety alerts.

1. List of drugs in which PIL was recommended.

S. No	Suspected drugs	Adverse drug reactions	Action taken by CDSCO/PvPI
1	Piperacillin and Tazobactam	Hypokalaemia Bronchospasm	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
2	Mannitol	Hypokalaemia	Cardiovascular & Renal committee recommended that CDSCO should request the State Drug Controllers to direct the manufacturers of the drug to include mannitol induced hypokalaemia in the corresponding package insert of the drug.
3	Rota-virus vaccine	Intussusception	Updated by the MAHs to include in PIL of the drug.
4	Rabies vaccine	Erythema multiforme	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
5	Ranitidine	Cardiac arrest	Gastroenterology Hepatology committee noted that, Signal Review Panel (SRP) after critical evaluation of the ADR concluded that the causal relationship between intravenous ranitidine and cardiac arrest can be established but no association can be established with effervescent tablet with available data. Product labelling information also refer that as with other H2 receptor antagonists bradycardia, AV block with injection only was mentioned in the package insert of Ranitidine IV marketed in UK. Committee recommended that CDSCO should request State Drugs Controllers to direct the manufacturers of the drug that same label should be incorporated in the package insert of Ranitidine IV product marketed in India.
6	Pulmonary surfactant	Pulmonary haemorrhage	Pulmonary Committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers of the drug to include pulmonary haemorrhage as ADR to the corresponding PIL of the drug.
7	Ceftriaxone	Stevens Johnson Syndrome (SJS)	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated SJS in the package insert of the drug.
8	Lamotrigine	Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	Neurology & Psychiatry committee recommended that CDSCO may request the State Drug Controllers to direct manufacturers of the drug to incorporate lamotrigine induced SJS/TEN in PIL of the drug.

9	Betamethasone	Photosensitivity reaction	Dermatology & Allergy committee noted that the misuse of steroids such as Betamethasone ointment formulations over the face is associated with the sensitive skin–Topical Steroid Dependent Faces (which may induce photosensitivity) and rarely contact allergy with photosensitivity. After detail deliberation, committee opined that more data may be obtained from PvPI, IPC in support of the the ADR- Betamethasone induced photosensitivity.
10	Azithromycin	Acute Generalised Exanthematosus Pustulosis (AGEP)	Antimicrobial & Antiviral Committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated AGEP in the package insert of the drug.
11	Cloxacillin	Acute Generalised Exanthematosus Pustulosis (AGEP)	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated AGEP in the package insert of the drug.
12	Sodium valproate	Gum hyperplasia	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
13	Itraconazole	Photosensitivity reaction	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated photosensitivity in the package insert of the drug.
14	Ibuprofen	Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)	Under consideration of CDSCO to include in PIL of the drug.
15	Amoxicillin/ Clavulanate Potassium	Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated SJS/TEN in the package insert of the drug.
16	Ciprofloxacin	Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated SJS/TEN in the package insert of the drug.
17	BCG vaccine	Lymphadenopathy	Under consideration of CDSCO to include in PIL of the drug.
18	Docetaxel	Candidiasis	Oncology & Rheumatology committee recommended that CDSCO should request the State Drug Controllers to direct the manufacturers of the drug to include Docetaxel associated candidiasis as an ADR in the corresponding PIL of the drug.

19	Phenytoin	Acute Generalised Exanthematosus Pustulosis (AGEP)	Neurology and Psychiatry committee agreed with the recommendation of SRP, PvPI to incorporate Phenytoin associated AGEP in the package insert of suspected drug.
20	Sulfasalazine	Stevens Johnson Syndrome (SJS)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
21	Sulfasalazine	Toxic Epidermal Necrolysis (TEN)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
22	Terbinafine	Acute Generalised Exanthematosus Pustulosis (AGEP)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
23	Dipeptidyl peptidase-4 (DPP-4) Inhibitors	Arthralgia	Endocrinology & Metabolism committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to include DPP-4 inhibitors induced arthralgia in the package insert of the drug.
24	Carbamazepine	Drug Reaction with Eosinophilia and Systemic Sypmtoms (DRESS) syndrome	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
25	Meropenem	Hypokalaemia	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
26	Artemether + Lumefantrine	Stevens Johnson Syndrome (SJS)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
27	Diclofenac	Nicolau syndrome	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
28	Lamivudine	Hearing loss	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
29	Amlodipine	Alopecia	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
30	Cefixime	Mouth ulceration	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
31	Carvedilol	Hyperkalaemia	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
32	Amlodipine	Gingival hypertrophy	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
33	Cefotaxime	Angioedema	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
34	Ofloxacin	Stevens Johnson Syndrome (SJS) /Toxic Epidermal Necrolysis (TEN)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PI of the drugL.

35	Tranexamic acid	Seizure/Convulsion	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
36	Quetiapine	Urinary incontinence	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
37	Sulfasalazine	Drug Reaction with Eosinophilia and Systemic Sypmtoms (DRESS) syndrome	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
38	Tramadol	Hiccups	Analgesic & Rheumatology committee recommended that the details of Individual Case Safety Reports (ICSRs) should be obtained from PvPI for further review by the Committee.
39	Phenobarbital	Drug Reaction with Eosinophilia and Systemic Sypmtoms (DRESS) syndrome	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
40	Cefepime	Urticaria	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
41	Glibenclamide	Palpitation	Endocrinology & Metabolism committee opined that palpitation is a known and reported symptom of hypoglycaemia associated with Glibenclamide which is already mentioned in package insert of Glibenclamide. It is not clear whether the palpitations as reported in 12 ICSRs are due to hypoglycaemia or otherwise. Therefore, further details in this regard should be obtained from NCC-PvPI for further consideration.
42	Chloroquine	Toxic Epidermal Necrolysis (TEN)/Stevens Johnson Syndrome (SJS)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
43	Proton Pump Inhibitors	Acute Kidney Injury	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL of the drug.
44	Alfuzosin	Palpitation	Cardiovascular & Renal committee recommended that CDSCO should request the State Drugs Controllers to direct the manufactures of the Alfuzosin formulation to include Palpitation as an ADR of the drug Alfuzosin in the package insert.
45	Benidipine	Photosensitivity reaction	Cardiovascular & Renal committee recommended that CDSCO should request the State Drugs Controllers to direct the manufactures of the Benidipine formulation to include photosensitivity as an ADR of the drug Benidipine in the package insert.
46	Pentoxifylline	Palpitation	Cardiovascular & Renal committee recommended that CDSCO should request the State Drugs Controllers to direct the manufactures of the Pentoxifylline formulation to include palpitation as an ADR of the drug Pentoxifylline in the package insert.
47	Piperacillin+Tazobactam	Acute Generalised Exanthematosus Pustulosis (AGEP)	117th committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include AGEP in package insert.
48	Tinidazole	Skin hyperpigmentation	Antimicrobial & Antiviral committee recommended that CDSCO should request the State Drugs Controllers to direct the manufactures of the Tinidazole formulation to include hyperpigmentation as an ADR of the drug Tinidazole to include in PIL.

49	Tramadol	Urinary retention	Analgesic & Rheumatology committee recommended that CDSCO should request the State Drug Controllers to direct the manufacturers of the drug to include urinary retention as ADR in the corresponding package insert of the drug.
50	Tigecycline	Coagulopathy	117th committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include Tigecycline associated coagulopathy as ADR in the corresponding PIL of the drug.
51	Olanzapine	Hyponatraemia	Neuro & Psychiatry committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include ADR of Olanzapine associated hyponatraemia in the package insert of the drug.
52	Haloperidol	Cogwheel rigidity	Neuro & Psychiatry committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include ADR of Haloperidol associated cogwheel rigidity in the package insert of the drug.
53	Remdesivir	Sinus bradycardia	117th committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include Remdesivir associated sinus bradycardia as ADR in the corresponding PIL of the drug.
54	Losartan	Muscle spasm	Committee recommended that CDSCO should request the State Drugs Controller to instruct the manufacturers of the drug to include muscle spasm as an ADR in the PIL of the drug.
55	Piroxicam	Fixed Drug Eruption (FDE)	Committee recommended that CDSCO should request the State Drugs Controllers to instruct the manufacturers of the drug to incorporate Piroxicam associated FDE in the PIL of the drug.

2. List of drugs in which changes in Drug Safety Label was recommended.

S. No	Suspected drugs	Adverse drug reactions	Action taken by CDSCO/PvPI
1	Carbamazepine	Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	The order has been issued by CDSCO to all State Drugs Controllers for Drug Safety Label Change – Patient may be screened for HLA- B*1502 prior to initiating the Carbamazepine treatment.

3. List of drugs in which signal was generated.

S. No	Suspected drugs	Adverse drug reactions	Action taken by CDSCO/PvPI
1.	Cefixime	Acute Generalised Exanthematosus Pustulosis (AGEP)	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL (Signal).
2.	Itraconazole	Acute Generalised Exanthematosus Pustulosis (AGEP)	Antimicrobial & Antiviral committee recommended that CDSCO should communicate the State Drugs Controllers to direct the manufacturers of the drug Itraconazole to include AGEP as a potential signal in the drug PIL.
3.	Furosemide	Dermatitis lichenoid	Reproductive & Urology committee agreed with the recommendation of Signal Review Panel (SRP), PvPI and update the package insert accordingly.
4.	Lithium carbonate	Drug Reaction with Eosinophilia and Systemic Sypmtoms (DRESS) syndrome	Neurology and Psychiatry committee agreed with the recommendation of SRP, PvPI to incorporate Lithium Carbonate associated DRESS in to the package insert of suspected drug.
5.	Fluconazole	Hyperpigmentation	The order has been issued by CDSCO to all State/UT Drugs Controllers to include in PIL (Signal).
6.	Oseltamivir	Sinus bradycardia/Brady cardia	117th committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include Oseltamivir associated sinus bradycardia/bradycardia as ADR in the corresponding PIL (Signal) of the drug.
7.	Tinidazole	Fixed eruption	Antimicrobial & Antiviral committee recommended that CDSCO may request the manufacturers of the drug to incorporate drug associated Fixed Drug Eruption in the package insert of the drug.
8.	Mefenamic acid	Fixed Drug Eruption (FDE)	Analgesic & Rheumatology committee recommended that CDSCO should request the State Drug Controllers to direct the manufacturers of the drug to include FDE as ADR in the corresponding package insert of the drug.
9.	Doxycycline	Fixed Drug Eruption (FDE)	Antimicrobial & Antiviral committee recommended that CDSCO may request State Drug Controllers to direct the manufacturers of the drug to incorporate drug associated Fixed Drug Eruption in the package insert of the drug.
10.	Minoxidil	Folliculitis	Under consideration of CDSCO to include in PIL (Signal).
11.	Cephalosporins	Fixed Drug Eruption (FDE)	117th committee recommended that CDSCO should request the State Drugs Controllers to direct the manufacturers to include Cephalosporin Class associated with FDE as ADR in the corresponding PIL (Signal) of the drugs.

12.	Paracetamol	Fixed Drug Eruption (FDE)	Committee recommended that CDSCO should request the State Drugs Controllers to instruct the manufacturers of the drug to incorporate Paracetamol associated FDE in the PIL (Signal) of the drug marketed in the country.

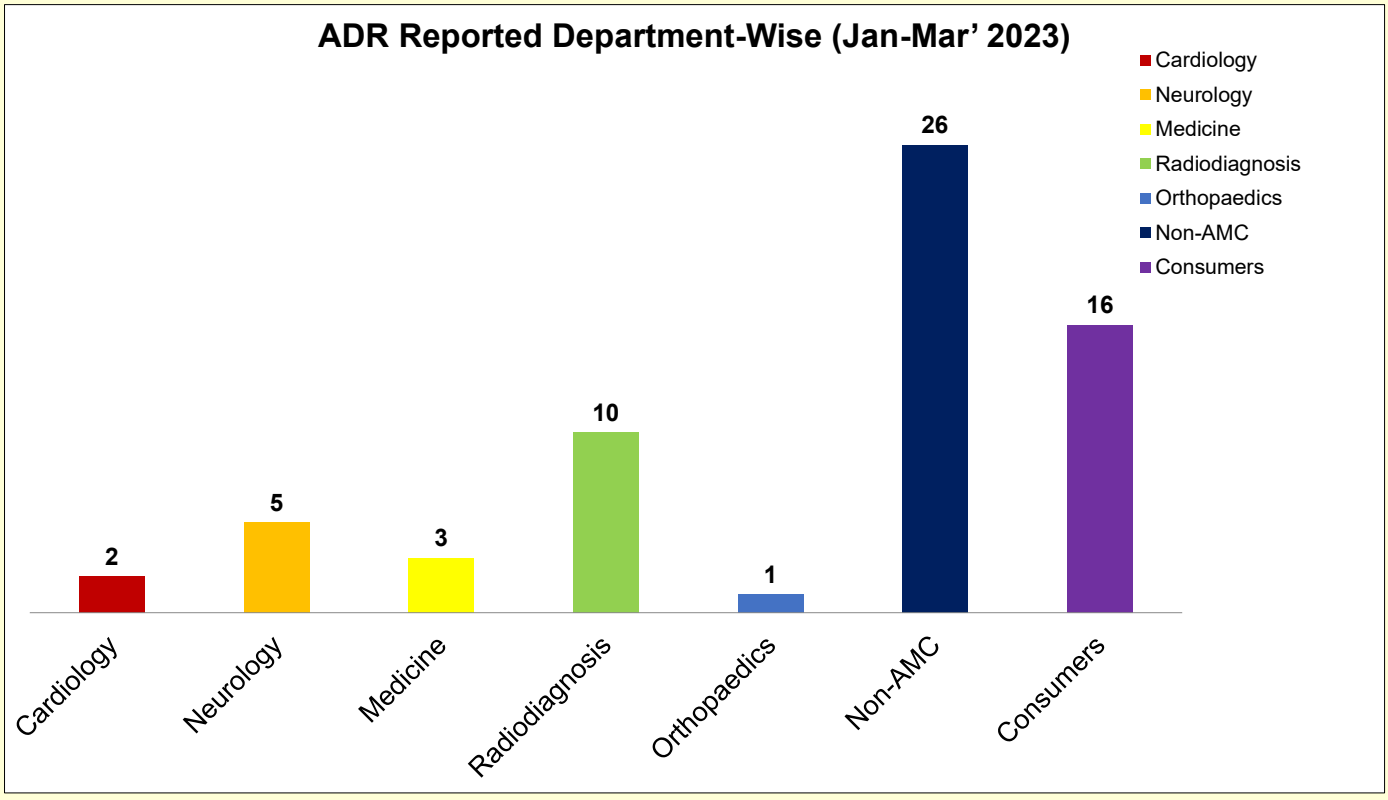
4. List of drugs in which drug safety alert was issued.

S. No	Suspected drugs	Adverse drug reactions	Action taken by CDSCO/PvPI
1.	Cefpodoxime	Drug Reaction with Eosinophilia and Systemic Sypmtoms (DRESS) syndrome	PvPI had issued Drug Safety Alert
2.	Zinc (Acetate/Oxide/ Sulphate/Gluconate)	Diarrhoea	PvPI had issued Drug Safety Alert

Reference:

https://www.ipc.gov.in/images/Updated_List_of_SRP_Reccomendations_to_CDSCO.pdf

ADRs reported by various departments of Dr. RMLIMS, Lucknow



Drug Safety Alerts (Jan-Mar 2023)

S.No.	Suspected Drugs	Indications	Adverse Drug Reactions
1.	Amphotericin B (Liposomal)	Febrile neutropenia in cancer patients For invasive fungal infection in patients who are refractory to or intolerant of conventional Amphotericin B therapy Treatment of visceral leishmaniasis	Hearing disorders Tachycardia
2.	Cephalosporins	Infections from gram-positive and gram-negative bacteria	Purpura
3	Amikacin	Treatment of serious infections due to Amikacin sensitive organisms	Vision blurred
4.	Metoprolol	Treatment of essential hypertension in adults, functional heart disorders, migraine prophylaxis, cardiac arrhythmias, prevention of cardiac death and reinfarction after the acute phase of myocardial infarction, stable symptomatic CHF	Hyponatraemia
5.	Nebivolol	Treatment of essential hypertension	Hyperkalaemia
6.	Olmesartan	Hypertension	Muscle spasm Taste disorder
7.	Sulfasalazine	Treatment of severe rheumatoid arthritis, ulcerative colitis and crohn's diseases	Visual impairment

Reference:
1. https://www.ipc.gov.in/images/Drug_Safety_Alert_January_2023.pdf
2. https://www.ipc.gov.in/images/Drug_Safety_Alert_February_2023.pdf
3. https://www.ipc.gov.in/images/Drug_Safety_Alert_March_2023.pdf

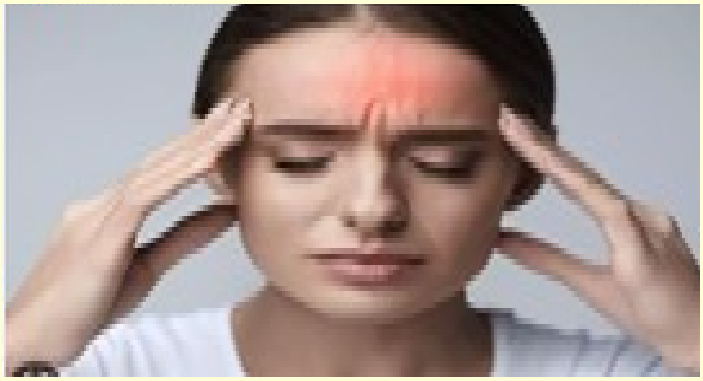
US-FDA Approved New Drugs (Jan-Mar 2023)

S.No.	Drug	Mechanism of Action	Indication	Date of approval
1	Lecanemab-irmb	It is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. It reduces amyloid beta plaques.	To treat Alzheimer's disease	6/1/2023
2	Bexagliflozin	It is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.	To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise	20/1/2023
3	Pirtobrutinib	It is a noncovalent inhibitor of Bruton's Tyrosine Kinase (BTK). BTK is a signaling protein of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.	To treat relapsed or refractory mantle cell lymphoma in adults	27/1/2023
4	Elacestrant	It is an estrogen receptor antagonist that binds to Estrogen Receptor-alpha (ER-α).It has antitumor activity including in ER+ HER2- breast cancer models resistant to fulvestrant and cyclin-dependent kinase 4/6 inhibitors and those harboring estrogen receptor 1 gene (ESR1) mutations.	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression	27/1/2023
5	Daprodustat	It is a reversible inhibitor of HIF-PH1, PH2 and PH3 (IC50 in the low nM range). This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin.	To treat anemia caused by chronic kidney disease for adults on dialysis for at least four months	1/2/2023
6	Velmanase alfa-tycv	Alpha-mannosidosis is a lysosomal storage disease due to deficiency of the enzyme alpha-mannosidase, caused by gene variants in Mannosidase Alpha Class 2B Member 1, that results in the intra-lysosomal accumulation of mannose-rich oligosaccharides in various tissues. Velmanase alfa-tycv provides an exogenous source of alphamannosidase.	To treat non-central nervous system manifestations of alpha-mannosidosis	16/2/2023

S.No.	Drug	Mechanism of Action	Indication	Date of approval
7	Sparsentan	It is a single molecule with antagonism of the endothelin type A receptor (ETAR) and the angiotensin II type 1 receptor (AT1R). Endothelin-1 and angiotensin II are thought to contribute to the pathogenesis of IgAN via the ETAR and AT1R, respectively.	To reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression	17/2/2023
8	Omaveloxolone	The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown. Omaveloxolone have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress.	To treat Friedrich's ataxia	28/2/2023
9	Zavegepant	It is a Calcitonin Gene-Related Peptide (CGRP) receptor antagonist.	To treat migraine	9/3/2023
10	Trofinetide	The mechanism by which trofinetide exerts therapeutic effects in patients with Rett syndrome is unknown.	To treat Rett syndrome	10/3/2023
11	Retifanlimab-dlw	Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Retifanlimab-dlwr binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2, and potentiates T-cell activity.	To treat metastatic or recurrent locally advanced merkel cell carcinoma	22/3/2023

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

ZAVEGEPANT (ZAVZPRET) NASAL SPRAY FOR ACUTE MIGRAINE



Migraine affects more than one billion individuals each year across the world, and is one of the most common neurologic disorders, with a high prevalence and morbidity, especially among young adults and females.

A migraine is a headache that can cause severe throbbing pain or a pulsing sensation, usually on one side of the head. It's often accompanied by nausea, vomiting, and extreme sensitivity to light and sound. Migraine attack can last for hours to days, and the pain can be so severe that it interferes with your daily activities.

Ubrogepant and Rimegepant are oral CGRP (Calcitonin Gene-Related Peptide) receptor antagonists were approved for the treatment of acute migraine. (BHV- 3500) Nasal spray (calcitonin gene-related peptide receptor antagonist) developed by Pfizer, recently approved for the acute treatment of migraine with or without aura in adults [1]. It was approved for medical use in the United States in March 2023 [2,3].

INDICATIONS AND USAGE

Acute treatment of migraine with or without aura in adults. It is not for the preventive treatment of migraine.

MECHANISM OF ACTION

It is a CGRP receptor antagonist. The pathophysiology of migraine has not been fully elucidated; however, specific vasoactive substances and neurotransmitters such as CGRP, neurokinin A, nitric oxide, and substance P may participate in the neurovascular and cortical spreading depression mechanisms. In acute migraine, the release of CGRP increases vasodilation and modulates neuronal excitability, which facilitates pain responses in structures for migraine pain transmission, such as the trigeminal system. Therefore, CGRP receptor antagonists such as zavegepant inhibit vasodilation mechanisms and desensitize neuronal circuits[4].

DOSAGE FORMS AND STRENGTHS

Nasal spray: 10 mg of zavegepant per device.

RECOMMENDED DOSE

10 mg (one spray) zavegepant is given in one nostril, as needed. The maximum dose that may be given in a 24-hour period is 10 mg (one spray). The safety of treating more than 8 migraines in a 30-day period has not been established.

PROTEIN BINDING
It has a plasma protein binding of approximately 90%[5].

HALF-LIFE
Following a 10 mg dose, it has an effective half-life of 6.55 hours[5].

METABOLISM
In vitro, it is mainly metabolized by CYP3A4, and by CYP2D6 to a lesser extent. After a single intravenous dose of [14C]-zavegepant (5 mg), approximately 90% of the circulating dose was unchanged. None of the metabolites detected in plasma were found at a proportion higher than 10% (no major metabolites)[5].

ROUTE OF ELIMINATION
Mainly excreted via the biliary/fecal route, while the renal route plays a minor role in its elimination. In healthy male subjects given a single dose of 5 mg [14C]-zavegepant intravenously, approximately 80% and 11% of the dose were recovered as unchanged in feces and urine, respectively[5].

CONTRAINDICATIONS
History of hypersensitivity reaction to zavegepant .

WARNINGS AND PRECAUTIONS
If a serious hypersensitivity reaction occurs, discontinue and initiate appropriate therapy. Hypersensitivity reactions including facial swelling and urticaria have occurred with zavegepant.

ADVERSE REACTIONS
Most common adverse reactions were taste disorders, nausea, nasal discomfort, and vomiting.

Reference:
1. ^ https://www.businesswire.com/news/home/20230309005795/en/Pfizer%E2%80%99s-ZAVZPRET%E2%84%A2-zavegepant-Migraine-Nasal-Spray-Receives-FDA-Approval
2. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/216386Orig1s000ltr.pdf
3. ^ https://www.businesswire.com/news/home/20230309005795/en/Pfizer%E2%80%99s-ZAVZPRET%E2%84%A2-zavegepant-Migraine-Nasal-Spray-Receives-FDA-Approval
4. https://go.drugbank.com/drugs/DB15688
5. https://labeling.pfizer.com/ShowLabeling.aspx?id=19471

Biotechnology: A novel tool of drug development

Biotechnology has significantly influenced the process of discovering and developing new drugs and has significantly enhanced human health and wellbeing. As a result there was improved understanding of the diseased signalling pathways that made it possible to identify the prospective therapeutic targets. Moreover, improvements in cell and molecular biology techniques allowed researchers to screen drugs quickly and to more effectively obtain information about their mechanisms of action and toxicity. This reduced drug failure rates and enhanced therapeutic results in long term effects. [1]

The fermentation approach, recombinant DNA technique, and hybridoma technique are just a few examples of the various biotechnologies that have been utilised to generate affordable diagnostics, repurpose current antivirals, find novel medications, and manufacture secure and reliable vaccines. [2] The number of biotechnologically derived medications that are now available to treat a wide range of illnesses, such as various cancers, diabetes mellitus, infectious diseases (i.e. AIDS virus/HIV), cardiovascular, neurological, respiratory, and autoimmune diseases, have increased exponentially in recent years. [3] Some of the best selling biotechnology drugs are listed in table 1. [4]

Table 1. List of major biotechnology drugs

S.No.	Name of drug	Type of drug	Generic name	Mechanism of action	Indications	Manufacturer
1	**Humira**	**Biologics**	**Adalimumab**	**Inhibits Tumour Necrosis Factor alfa (TNF-alfa)**	**Rheumatoid arthritis Plaque psoriasis Crohn's disease Pediatric crohn's disease Ulcerative colitis Psoriatic arthritis Ankylosing spondylitis Polyarticular juvenile idiopathic arthritis**	**AbbVie**
2	**Remicade**	**Immunosuppresant**	**Infliximab**	**Disrupts the interaction of TNF – alfa with its receptor & also cause lysis of cells that produce TNF - alfa**	**Rheumatoid arthritis Psoriatic arthritis Crohn's disease Ulcerative colitis Chronic plaque psoriasis**	**Johnson & Johnson`**

3	**Rituxan**	**Monoclonal antibody**	**Rituximab**	**Binds to CD 20 cells cause cell mediated cytotoxicity & antibody dependent cell mediated cytotoxicity**	**Rheumatoid arthritis Non-Hodgkin Lymphoma (NHL) Chronic Lymphocytic Leukemia (CLL) Granulomatosis with polyangiitis Microscopic polyangiitis**	**Biogen Roche**
4	**Enbrel**	**Biologic**	**Etanercept**	**TNF- alfa inhibitor and decrease cytokine storm**	**Rheumatoid arthritis Polyarticular juvenile Idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis**	**Amgen**
5	**Lantus**	**Insulin**	**Long acting insulin**	**Lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle & fat & by inhibitinghepati c glucose production**	**Diabetes**	**Sanofi**
6	**Avastin**	**Angiogenesis inhibitors**	**Bevacizumab**	**Humanized monoclonal IgG antibody & inhibits angiogenesis by binding & neutralizing VEGF-A**	**Glioblastoma Metastatic colorectal cancer Non–small cell lung cancer Metastatic kidney cancer Advanced cervical cancer Platinum-resistant ovarian cancer**	**Roche**

7	**Herceptin**	**Monoclonal antibody**	**Trastuzumab**	**Monoclonal antibody against human epidermal growth factor receptor – 2 (HER-2) , prevents HER-2 homodimerization & prevents HER-2 mediated signalling**	**Breast cancer Metastatic stomach/ Gastroesophageal Junction (GEJ) cancer**	**Roche**
8	**Neulasta**	**Colony stimulating factor**	**Pegfilgrastim**	**Recombinant human granulocyte Colony stimulating factor stimulate the production of neutrophils**	**Infections during chemotherapy**	**Amgen**
9	**Prevnar**	**Inactivated bacterial vaccine**	**Pneumococcal conjugate vaccine**	**Produce T- cell dependent immune response & promotes bacterial opsonization & phagocytosis**	**Pneumococcal pneumonia**	**Pfizer**
10	**Avonex**	**Immunomodulatory**	**Interferon beta- 1a**	**Balances the expression of pro & anti-inflammatory agents in the brain & prevents nerve damage**	**Multiple sclerosis**	**Biogen**

Moreover, genetically modified organisms that can be purposefully released into the environment for disease vectors like mosquito control can be made via biotechnology. For instance, developments in genome engineering technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated protein 9 (Cas9), have made it possible to create gene drives, a method that enables desired genetic alterations to spread more quickly throughout a population over a number of generations. Cervical cancer is the second most fatal type of cancer for women after breast cancer. It kills 2,75,000 women each year. Therefore vaccine is crucial for it. So, the U.S. Food and Drug Administration (FDA) has recently licenced two vaccines Cervarix and Gardasil for use in women between the ages of 9 and 26.

Thanks to the sequencing of the malarial genome that the medicine Fosmidomycin has entered clinical trials for the treatment of malaria in less than two years as a result of the genome sequencing of the malaria parasite Plasmodium falciparum. A thorough analysis of the parasite's DNA found that it contained an enzyme that is known to be stopped by the antibiotic Fosmidomycin, which had already been licenced to treat urinary infections. [5]

Recombinant DNA technology, genetic engineering, antisense technology to treat genetic diseases are the main lures of biotechnology. Examples of Recombinant DNA technology are human insulin, human growth hormone, alpha interferon, hepatitis B vaccine. Drug developed through genetic engineering are insulin, human growth hormones, follistim, human albumin, antihemophilic factors, vaccines. Commonly used monoclonal antibodies are Rituximab for Chronic Lymphocytic Leukaemia (CLL), Cetuximab for treatment of advanced bowel cancer and head and neck cancer and Trastuzumab for breast cancer.

Current commercial medication research and development heavily relies on a variety of vaccinations, including live attenuated, inactivated, subunit, toxoid, conjugate DNA, and recombinant vector vaccines. The pharmaceutical sector can create new goods, processes, procedures, and services with the use of biotechnology, as well as enhance already existing ones. Nowadays, biopharmaceuticals account for about 18% of medicine sales. India is ranked amongst the top 12 biotech destinations in the world and ranks 3rd in Asia. [6,7]

Biotechnological advances made possible by science can help with issues like halting the spread of infectious illnesses, alleviating hunger, and repairing environmental damage. Gene therapy holds promise for treating a wide range of diseases, such as cancer, cystic fibrosis, heart disease, diabetes, hemophilia and AIDS. Animals may be used to develop human organs that can then be transplanted into humans. Gene therapy is evolving so quickly, though, its safety is not yet known. We need to find ethical solutions to the problems with how we treat animals. [8]

The regulation of genetic engineering refers to the methods used by governments to evaluate and manage the dangers posed by the application of genetic engineering technology, as well as the creation and release of Genetically Modified Organisms (GMO), such as genetically modified fish and crops. There are regional variations in GMO regulation, with the US and Europe having some of the most pronounced variations. Depending on how a given country intends to use the genetic engineering products, different regulations apply. In accordance with the U.S. Coordinated Framework for the Regulation of Biotechnology, the FDA regulates plant and animal biotechnology products in collaboration with the U.S. Department of Agriculture (USDA) and U.S. Environmental Protection Agency (EPA). Each of these regulatory bodies has created regulations and guidelines to carry out its legal obligations and to support the safety and, when appropriate, the efficacy of biotechnology goods. According to the provisions of the Bill tabled in the Parliament in 2013, the Biotechnology Regulatory Authority of India (BRAI) is a planned regulatory organisation to control the use of GMOs. India has signed the Cartagena Protocol, and the protocol requires the establishment of a regulatory body, hence BRAI was required. There are no common mandated international biosafety and biosecurity standards that all research labs must follow with, and there is no system in place that establishes responsibility or established procedures for evaluating liability claims when operations go wrong. These international structures are ill-prepared to deal with risks brought on by advances in biotechnology. [9]

The long-term effects of changing the genetic makeup of several creatures, including microorganisms used in the pharmaceutical sector, animals used in biological research, and plants used in agriculture, are still unknown. The ecology in nature may become out of balance if GMOs, particularly transgenic microbes, escape into the wild. The biodiversity, also known as variety, of species may decline as a result of this. As the capacity to change a person's characteristics and skills both before and after birth grows, there will likely be disagreement over the bounds and ramifications of tampering with human biology.

Greater control and predictability over human form and behaviour may be made possible by biotechnology, enabling for specialisation to confer machine interface compatibility, personal reproductive or performance advantage, or to affect large-scale social change. Support for its implementation is probably going to grow as a result of the promise of better health and longevity, but it is also going to raise questions about how societies should get ready to handle a population that's considerably healthier and lives longer. Human biotech modification could lead to medical reliance and non-medical benefits.

The international community must work together to create standards that regulate experiment safety and security, create the BWC's long-debated verification and monitoring system, and include provisions that establish liability and accountability mechanisms in the event of violations if responsible biotechnology research is to be conducted. The federal government should create and put into action a long-term risk analysis strategy for upcoming biotechnology products that is focused on identifying and prioritising key risks for less familiar and more complicated biotechnology products. It should also work to establish appropriate federal funding levels for ongoing, multiyear research to create the necessary advancements in regulatory science.

In order to ensure consumer and workplace safety associated with new biotechnology products, EPA, FDA, and USFDA should collaborate with federal and state consumer- and occupational-safety regulators that may come into contact with them in the upcoming five to ten years. They should also use pilot projects, interagency collaborations, shared data resources, and scientific tools to pilot new approaches for risk assessment, particularly those that may involve novel financing mechanisms or in other means to make sure that new biotechnology goods are safe for consumers and workers, especially if they may entail novel funding methods, production processes, or distribution channels . [10] These actions would significantly improve the likelihood that the world can benefit from biotechnology advancements while minimising the dangers and drawbacks.

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