ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 15th issue of ESSENCE.

Improper disposal of unused/expired medicines can have a harmful impact on the environment, occurrence of resistance (drug resistance organisms), occurrence of diseases among animals/fishes following environmental exposure (Eco-pharmacology). Proper disposal of these expired drugs is absolutely essential and the current issue deals with this important concern.

As many of the Biopharmaceuticals come off patent, there is a flood of Biosimilars ready to tap the market. The current issue has a very relevant article talking about the various aspects of Biosimilars and their place in the modern therapy.

Drug treatment during pregnancy is hazardous because of the physiologic changes in the mother and the risk of teratogenic consequences to the foetus. There are various issues involving the use of drugs in pregnancy and in this issue, we have a guest column highlighting this aspect.

Further, as always, we have recent news from the world of medicines, new drug approvals, Drug safety alerts and cross word puzzle.

Happy Reading.

Jai Hind.

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

Safe disposal of unused/expired medicines:

What is expiration date?

The self-life concept was made a mandate by the Food and Drug Administration (FDA) in 1979, and it is to be written on the container label. Later on, the same was endorsed by ICH (International conference on harmonization) in Q1a and Q1E documents. The expiry date represents the last date till which, the manufacturer guarantees the drug content and approved specifications. Among all the agents, solid dosage forms (capsule, tablet) are the most stable, however, this may not be the case in case of reconstituted suspension. Although there are many debates about effectiveness of drugs after their expiry date, however, the WHO guidelines highlight that expired drug must be disposed of safely.

Problems with unused and expired medicines:

As the population burden is increasing, the burden of unused or expired medicine is also increasing along with their environmental spillover or contamination and accidental intake. Improper disposal of unused/expired medicines can have a harmful impact on the environment, occurrence of resistance (drug resistance organisms), occurrence of diseases among animals/fishes following environmental exposure (eco-pharmacology).

How to deal with expired medicines?

The common civilian practice to expired medicines is disposal as per appropriate guidelines. The WHO guidelines highlight that expired drug must be disposed safely. However, the military needs to maintain stocks of medicines for any emergency/CBRN (Chemical, biological, radiological and nuclear) attack, the maintenance cost of which is huge. The expiry of medicines becomes a further burden on the same. In this case, the United States department of defense (US-DOD) and Food and Drugs administration (FDA) runs a program named SLEP (Self life extension Program), where after testing the drugs for stability, drug assay, disintegration and dissolution profile, if the batch of specific regulatory requirements as per US Pharmacopoeia, the self-life of the drug can be extended. Such programs are well established in case of emergency drugs like potassium iodide (in case of nuclear attack), Ciprofloxacin and doxycycline (for bioterrorism). At this current point of time, the SLEP can be initiated by DOD-SLEP program or by the manufacturer.

Dealing with unused/expired medicines: the USFDA perspective:

The best way to deal with most of unused/expired medicines is to return back the medicines to appropriate authority through appropriate “drug-take back programs”, where, different drug take-back sites [either permanent or temporary/periodic]. However, all medicines which are dropped into the drug take back sites will be destroyed.

Flush drugs:

In case drug-take back programs are not available, the drug can be disposed of by flushing in toilet, if the drug in FDAs “flush list”.

Disposal instructions in package insert:

In these cases, important drug disposal instructions are provided in the package insert.

No drug take-back sites, drug not in flush list and no specific disposal instruction in package-insert:

In this situation, the FDA encourages mixing the medicines with some unpalatable materials (e.g., used coffee

grounds, cat litter etc.), which can then be enclosed in a sealed plastic bag and discarded. In case of medicine bottles or container, the container label is to be deleted before putting the bottle in the trash.

Private endeavors:

There are many private endeavors which deal with the unused/expired medicines. One such endeavor is Rx return services, where they give appropriate return to the customers in exchange of unused/expired medicines and pays as per the quality of the product. In case of products which are not usable, they are destroyed. Other such services are Safe Medication Return Program of Washington state department of health, return solutions etc.

WHO guidelines on disposal of expired medicines:

The WHO recommended disposal methods are return to donor or manufacturer, Landfill, waste encapsulation, Inertization, sewer (fast flowing water course) and medium to high temperature incineration. WHO recommends different types of treatments for different types of pharmaceutical preparations e.g., anti-infective drugs can be encapsulated, inertized or incinerated. In case of liquid antibiotics, it can be diluted in water than left as such for weeks, which can then be discarded in sewer. Antineoplastics are not be disposed by landfill unless encapsulated and not to be disposed by sewer.
Low temperature incineration is not recommended, rather medium and high temperature incineration is recommended. Liquids can be disposed through sewer or high temperature incineration. Ampoules can be cursed and the diluted solution can be disposed through sewer except antineoplastics.

The Indian guideline: Bio Medical Waste Management Rules 2016:

As per this guideline (2), discarded and expired medicines and pharmaceutical waste e.g. cytotoxic drugs, antibiotics are to be kept in non-chlorinated yellow coloured plastic containers/bags. Cytotoxic drugs are to be handled by authorized persons only. The cytotoxic drugs are either to be returned back to manufacturer/supplier or a sent to biomedical waste treatment facility for incineration, plasma pyrolysis or encapsulation. Glasswares contaminated with cytotoxic drugs are to be disinfected with sodium hypochlorite and detergent and microwaving/autoclaving and then to be sent for recycling. Other discarded medicines are also handled in the same way e.g., either sent back to manufacturer or for incineration in a biomedical waste facility.

Conclusion: Adherence to the biomedical waste guidelines for safe disposal of unused/expired medicines may provide a better tomorrow by decreasing environmental contaminations and accidental drug use related incidents especially among children and drug abusers.

References:

1. Guidelines_for_Expired_Medicines.pdf [Internet]. [cited 2022 Apr 29]. Available from: http://www.emro.who.int/images/stories/pakistan/documents/pak_documents/Guidelines_for_Expired_Medicines.pdf

2. Bio Medical Waste Management Rules - 2016 | Department of Health Research | MoHFW | Government of India [Internet]. [cited 2022 Apr 29]. Available from: https://dhr.gov.in/document/guidelines/bio-medical-waste-management-rules-2016

Recent new/Update from the world of medicines ….

Reduced risk for parkinsonism in patients who take Statins

Statins may protect against age-related parkinsonism, as per a study published in the journal Neurology published on Mar 23. The observational study showed older adults taking statins had a lower risk for parkinsonism than their counterparts not taking statins. The findings are based on 2841 older adults with average age of 76 years with 75% being women. None had parkinsonism at the start of the study. They found statin use prior to death was associated with 37% lower odds of cerebral atherosclerosis compared with no statin use prior to death

The researcher's hypothesis that this effect is in part mediated by less severe intracranial atherosclerosis in statin users supporting the idea that cerebrovascular disease pathologies accumulating in older brains may be an unrecognized contributor to the common occurrence of parkinsonism in old age.

Proton Pump Inhibitors should be used 'Judiciously' in patients with Cirrhosis

Proton Pump Inhibitors (PPIs) are one of the most commonly used medications and they are frequently prescribed to Cirrhosis patients. In a retrospective study to evaluate the impact of proton pump inhibitors (PPIs) on all-cause mortality in patients with cirrhosis, researchers found PPIs were associated with a 23% increase in liver-related mortality. Further analysis suggested that the mortality increase could be related to a 21% increased risk for severe infection with PPI exposure in patients with cirrhosis, as well as a 64% increased risk for decompensation. The research was published online April 6 in the journal Gastroenterology.

PPI exposure in patients without gastrointestinal bleeding was associated with an increased risk for liver-related mortality, at a hazard ratio of 1.23, but a reduced risk for non-liver-related mortality, at a hazard ratio of 0.88. The authors note that the half-life of PPIs is "prolonged in patients with cirrhosis" and that alterations in the gastrointestinal microbiota as a result of gastric acid suppression "may allow for bacterial overgrowth and translocation," thus increasing the risk for infections. The results of the study underscore the importance of using PPIs judiciously in patients of cirrhosis and to be used only with compelling indications.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Ibuprofen	Fixed Drug Reaction
2.	Losartan	Muscle Spasm
3.	Hydrocortisone	Hypertrophic cardiomyopathy in neonates and infants
4.	Denosumab	Atypical fracture in non-femur sites
5.	Cefoperazone and sulbactam	Acute coronary syndrome accompanying allergic reaction
6.	Ivermectin	Disturbed consciousness

Biopharmaceutical drugs are an essential part of modern pharmacotherapy. These comprise proteins derived from recombinant DNA technology and hybridoma technique. Biological proteins (cytokines, hormones, and clotting factors), monoclonal antibodies, vaccinations, and cell and tissue-based therapies are only some of the examples. In the next several years, biopharmaceuticals have the potential to capture up to 50% of the worldwide pharmaceutical market. The expiration of patent protection for many biopharmaceuticals has sparked the creation of biosimilars, which are generic counterparts of innovator biopharmaceuticals. These biological products are regarded similar but not generic analogues of innovator biopharmaceuticals due to structural and manufacturing complexity. The term "biosimilar" is in common use in the European Union, while the term "follow on biologics" is more popular in the American context and “subsequent entry biologicals” in Japan.

Difference between biosimilars and chemical generics:

Chemical Generics	Biosimilars
Structurally well defined- well characterised one-dimensional structure.	Fragile and complex three-dimensional structure.
Low molecular weight	High molecular weight
Small molecular size	100 to 1000 times larger molecular size
Easy to reproduce and specify by mass spectroscopy and other techniques	Lack of appropriate investigative tools for specification.
Manufacturing processes are relatively simple	Manufacturing processes are relatively complex
Access to manufacturing processes of innovator products	No access to manufacturing processes of innovator products
Heterogenicity will be far less	Heterogenicity will be the major problem
Less immunogenic potential	Immunogenic potential will be unique safety issue
Low molecular weight	High molecular weight

The important issues of Biosimilars:

A. Efficacy Issue:

The efficacy issues for biosimilars are the difference between bioactivity of biosimilars, the difference between quality parameters like identity, purity and content, and the significant differences in biosimilar and originator product comparability

B. Safety Issue:

Immunological safety is one of the major concerns of biosimilars. Only cohorts of individuals participated in clinical trials and post-marketing surveillance can demonstrate immunological safety. Few examples of safety issues are:

1. A rise in the frequency of cases of pure red cell aplasia linked to a specific formulation of epoetin alfa biosimilar, Eprex raises concerns about immunogenicity. The development of neutralizing antibodies against endogenous epoetin induced the immunological form of pure red cell aplasia. Subtle adjustments in the

production process was most likely to blame. Polysorbate 80 and glycine were used to replace the human albumin stabilizer in the Eprex formulation. Polysorbate 80 is thought to have exacerbated Eprex immunogenicity by inducing the development of epoetin-containing micelles or interacting with leachates generated by prefilled syringes' uncoated rubber stoppers.

2. Treatment-associated thrombocytopenia was discovered in 13 of 325 healthy volunteers during clinical studies of pegylated thrombopoietin (megakaryocyte growth and development factor).

Preclinical data may be insufficient to confirm immunologic safety of some biosimilars. High affinity antibodies can also be detected using the radio immune precipitation assay and the double antigen bridging ELISA technique. However, these assays must be validated and standardized.

C. Pharmacovigilance

Vigorous pharmacovigilance is required due to the inadequate clinical database at the time of biosimilar licensure. With biosimilars, immunogenicity is a unique safety concern. However, the lack of validation and standardization of procedures for detecting immunogenicity suggests that considerable pharmacovigilance is required. The monitoring data for adverse medication responses should be comprehensive, including the type of adverse event and information about the medicine, such as the proprietary name, the international nonproprietary name (INN), and the dosage provided.

D. Substitution

Substitution of chemical pharmaceuticals permits generic drugs to be prescribed instead of innovator products; the logic behind substitution is that the original drugs and their generics are equivalent and have the same therapeutic effect. While automated substitution is appropriate for the majority of chemical generics and can save money, it should not be used for biosimilars since it could compromise therapy safety or result in therapeutic failure.

E. Naming and Labelling

The medicinal products are referred to as INN in technical terms. Because they are identical replicas of the reference items, generic adaptations of chemical medications are given the same name. Biosimilars, on the other hand, require unique INNs in order to ease biopharmaceutical prescribing and dispensing, as well as precision pharmacovigilance. Biosimilars should have complete labelling that includes differences from the original product as well as unique safety and efficacy data to help physicians and pharmacists make educated judgments.

F. Regulatory Approval

Unlike chemical generics, biosimilars require more strict quality, safety, and efficacy evaluation requirements. The European Parliament issued proposals for biosimilar regulatory approval in May 2004. In February 2006, the European Medicines Agency (EMEA) issued guidelines outlining clinical, nonclinical, and quality standards for biosimilars. The law prohibiting the substitution of one biological drug for another was likewise enacted by French legislation and the Spanish Ministry of Health and Consumer Affairs. The US Food and Drug Administration (FDA) and several other regulatory agencies are still working on developing rules for biosimilar marketing authorization.

To conclude, biosimilar will play a significant role in the future healthcare scene. As patents on innovator items expire, they will become more widely available. For accurate prescription and patient safety, understanding the differences between biosimilars and originator drugs in terms of efficacy, safety, and immunogenicity is critical.

New Drug Approvals…

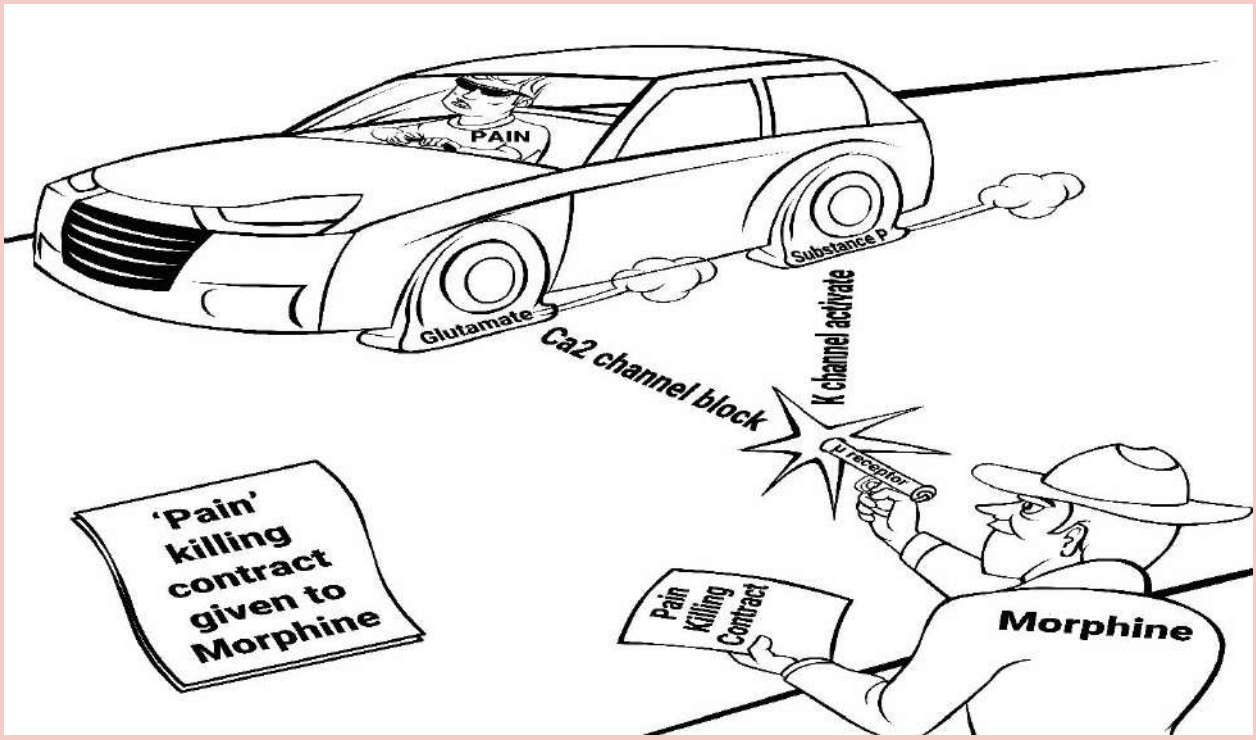
Abrocitinib is a Janus kinase (JAK) inhibitor approved for the treatment of adults with refractory, moderate-to-severe atopic dermatitis. The recommended dose is 100 mg orally once daily.

Faricimab is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor approved for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME), The recommended dose is 6 mg administered by intravitreal injection every 4 weeks.

Mitapivat is a pyruvate kinase activator approved for the treatment of hemolytic anemia in pyruvate kinase deficiency. The recommended dose is 5 mg orally twice daily.

Efgartigimod alfa is a neonatal Fc receptor blocker approved for the treatment of generalized myasthenia gravis. The recommended dose is 10 mg/kg administered as an intravenous infusion weekly for 4 weeks.

Cartoon Corner…



Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

GUEST COLUMN: Drug safety during pregnancy: A point to ponder!

Drug treatment during pregnancy is hazardous because of the risk of teratogenic consequences and physiologic changes in the mother. The pharmacokinetics of drugs taken are affected by pregnant physiology, and certain pharmaceuticals can reach the fetus and cause harm. Historical events such as the thalidomide crisis in the 1960s and the teratogenic effects linked to the use of diethylstilboestrol in 1971 have affected the concern about pharmaceutical usage during pregnancy and breastfeeding.

Effects of drug use during pregnancy

Not all maternal medicines make through to the foetus through the placenta. Some medications that pass the placenta have the potential to be directly harmful or teratogenic. Drugs that do not cross the placenta may still harm the foetus by constricting placental vessels, thus impairing gas and nutrient exchange, producing uterine hypertonia that results in anoxic injury and by altering maternal physiology. Whether and how quickly a drug crosses the placenta depends on the drug's molecular weight, the extent of its binding to a carrier protein, the area available for exchange across the placental villi, and the amount of drug metabolised by the placenta.

A drug's effect on the foetus is determined largely by fetal age at exposure, placental permeability, drug potency, and drug dosage and maternal factors such as drug absorption, distribution, metabolism, and excretion.

Fetal age affects the type of drug effect as follows:

- **Before the 20th day after fertilization:** Drugs given at this time typically have an all-or-nothing effect, killing the embryo or not affecting it at all. Teratogenesis is unlikely during this stage.
- **During organogenesis (between 20 and 56 days after fertilization):** Teratogenesis is most likely at this stage. Drugs that reach the embryo at this stage can cause spontaneous abortion, a sublethal gross anatomic defect (true teratogenic effect), covert embryopathy (a permanent subtle metabolic or functional defect that can manifest later in life), an increased risk of childhood cancer, or have no effect at all.
- **After organogenesis (in the 2nd and 3rd trimesters):** Drugs may disrupt the growth and function of normally formed foetal organs and tissues, but teratogenesis is uncommon. To cause harmful foetal consequences, doses must be increased as placental metabolism grows.

FDA Approval for Use of Medications in Pregnancy: An Uphill Battle

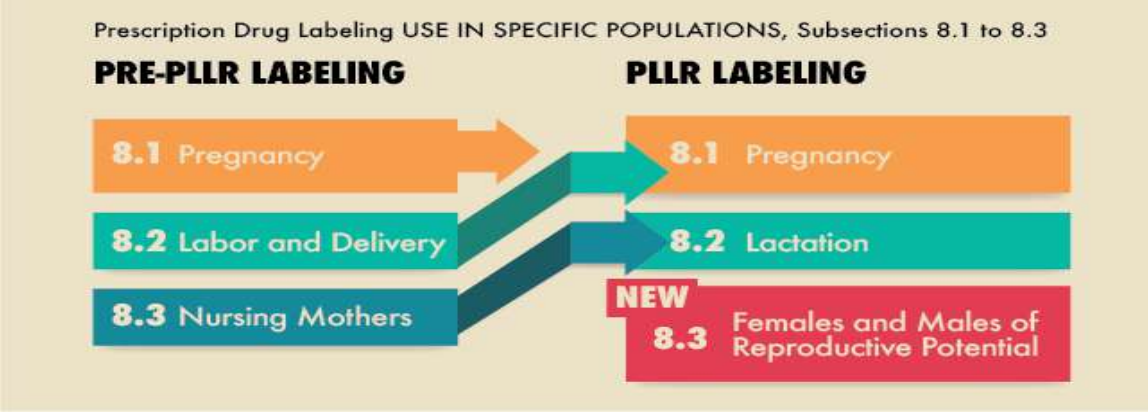
The FDA's medicine approval procedure is complicated, costly, and time-consuming. Before entering clinical trials, potential medications must first be found, purified, described, and tested in the laboratory (in cell and animal research). In total, around 1000 candidate medications are investigated before one is evaluated in a clinical study. This is a particularly difficult challenge during pregnancy. The FDA approval procedure for a drug's use during pregnancy involves a variety of specific hurdles and obstacles, including Pregnant women's reluctance to participate in scientific studies due to concerns about the health of their unborn baby; health pharmaceutical businesses have a limited market in pregnant women, and Drug developers and manufacturers are concerned about medicolegal responsibility. Hence, the FDA Approval for the use of Medications in Pregnancy can definitely be considered as An Uphill Battle.

FDA Pregnancy Risk Information: An Update

- Though there is an increasing trend in the use of drugs in pregnancy, there is lack of firm evidence-based guidelines for usage of all the drugs during pregnancy.
- We all are aware that the FDA classified over-the-counter (OTC) and prescription drugs into 5 categories of safety for use during pregnancy (A, B, C, D, X). However, few well-controlled studies of therapeutic drugs have been done in pregnant women.
- Most information about drug safety during pregnancy is derived from animal studies, uncontrolled studies, and post marketing surveillance. Consequently, the FDA classification system led to confusion and difficulty applying available information to clinical decisions.
- FDA now requires that labeling provide information about the specific drug in a consistent format called the final rule, or Pregnancy and Lactation Labeling (Drugs) Final Rule [PLLR].

Regulatory information about drug safety during pregnancy: Pregnancy and Lactation Labelling (Drugs) Final Rule [PLLR]

- The PLLR eliminates the pregnancy letter classifications of A, B, C, D, and X.
- The FDA requires information in three subsections.
- The following table compares existing prescription medicine labelling to the new PLLR labelling regulations.



Pregnancy subsection (8.1):

- Information relevant to the use of the drug in pregnant women (e.g., dosing, fetal risks) and includes information for a pregnancy exposure registry for the drug when available. Registries for pregnancy exposure collect and keep information on the effects of authorized medications prescribed to and taken by pregnant women.
- The "Pregnancy" subsection now includes information previously found in the "Labor and Delivery" subsection.
- A Pregnancy exposure register, Risk Summary, Clinical considerations, and Data are all included in the Pregnancy sub-section.

Lactation subsection (8.2):

- The Nursing mother's subsection has been renamed, the **Lactation** subsection (8.2)
- It includes details on how to use the drug while breastfeeding, such as the amount of drug in breast milk and the potential effects on the breastfed child.
- Information in the Lactation sub-section includes Risk Summary, Clinical considerations, and Data.

Females and Males of Reproductive Potential subsection (8.3)

- This part, which is new to the labelling, contains information regarding the need for pregnancy testing, contraception recommendations, and information about infertility as it applies to the drug, when applicable.
- Labeling for over-the-counter (OTC) medicines has not been changed and OTC drug products are not affected by the final rule. The PLLR also requires the label to be updated when information becomes outdated. For pregnant women seeking pharmacological therapy, the new labelling approach allows for improved patient-specific counselling and informed decision-making.
- While the new labelling is an improvement over the old style, it still does not provide a clear "yes" or "no" answer in the majority of circumstances. On a case-by-case basis, clinical interpretation is still required.
- On June 30, 2015, the Pregnancy and Lactation Labeling Final Rule (PLLR) went into force. The following are a few examples of medications licensed since June 30, 2015 that have new pregnancy and lactation subsections in their labels:
    - Flibanserin - for premenopausal women with generalized hypoactive sexual desire disorder (HSDD);
    - Emtricitabine and tenofovir alafenamide fumarate - for HIV-1 infection;
    - Sacubitril and Valsartan - for heart failure.
    - Ledipasvir and Sofosbuvir Are used to treat chronic viral hepatitis C. (HCV).
    - Alirocumab - for patients with heterozygous familial hypercholesterolemia or atherosclerotic heart disease.

Conclusion

Despite widespread concern about drug safety, exposure to therapeutic drugs accounts for < 2 to 3% of all fetal congenital malformations; most malformations result from genetic, environmental, multifactorial, or unknown causes. Additional programs are required to facilitate drug development for pregnancy-specific disorders and to accelerate and modernize the approval process. Creative solutions will need to be found, without affecting patient safety.

References

1. FDA/CDER SBIA Chronicles. Drugs in Pregnancy and Lactation: Improved Benefit-Risk Information. Accessed August 1, 2019 at https://www.fda.gov/files/drugs/published/%22Drugs-in-Pregnancy-and-Lactation--Improved-Benefit-Risk-Information%22-January-22--2015-Issue.pdf

Contributed by:

Dr. Sharmila Arun Babu

Additional Professor and Head,

Department of OBG, AIIMS Mangalagiri.

Dr. Pragati Trigunait,

Assistant Professor,

Department of OBG, AIIMS Mangalagiri.

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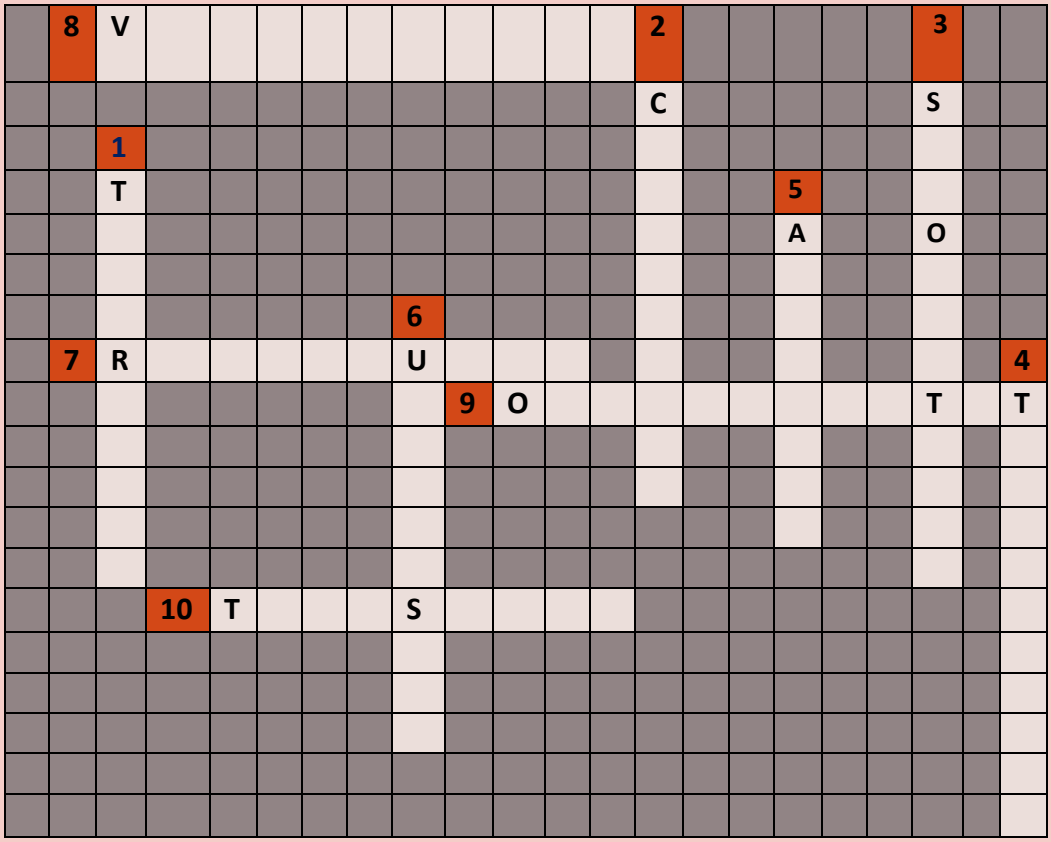
Crossword Puzzle…



Downward	Across
1. An antiepileptic agent, also prevent migraine attacks and cause lose weight, change in the taste of carbonated beverages. 2. A β blocker of choice in patients with peripheral artery disease? 3. A Dual PPAR Agonist approved for both diabetes and dyslipidemia in India? 4. A melatonin agonist approved for non-24-hour sleep-wake disorder in totally blind? 5. A drug that inhibits thromboxane synthesis but not inhibit thromboxane synthetase? 6. A selective progesterone receptor modulator used as an emergency contraceptive pill?	7. The first-in-class Oral agent which directly activates soluble guanylate cyclase (sGC) used or treatment of Pulmonary arterial hypertension? 8. A partial agonist at NICOTINE α4β2 receptors, the principal nicotinic receptor subtype involved in nicotine addiction? 9. An aldosterone synthase inhibitor indicated for the treatment of Cushing syndrome? 10. A drug used for constipation dominant IBS banned in India due to increased incidences of Myocardial infarction and stroke?

Answers:

Downward

1. Topiramate 2. Carvedilol 3. Saroglitazar 4. Tasimelteon 5. Aspirin 6. Ulipristol

Across

7. Riociguat 8. Varenicline 9. Osilodrostat 10. Tegaserod

Prepared by:
Mr. Santenna Chenchula
Tutor, Department of Pharmacology
AIIMS, Mangalagiri