Drug & Poison Information Center Bulletin
Faculty of Pharmacy - Tanta University

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FDA approves Allecra's Exblifep for complicated urinary tract infections treatment

The US Food and Drug Administration (FDA) has approved allerca therapeutics' exblifep (cefepime/enmetazobactam) to treat complicated urinary tract infections (cUTIs) including pyelonephritis. The approval is accompanied by a five-year marketing exclusivity extension from the US regulator under the Generating Antibiotic Incentives Now (GAIN) Act. The GAIN Act offers incentives for developing new anti-infective drugs by granting benefits to qualified infectious disease product manufacturers. The FDA granted the approval based on comprehensive clinical data highlighting the effectiveness of exblifep against antimicrobial resistance in gram-negative bacteria, particularly resistance caused by extended spectrum beta lactamases and ampC enzymes.

What is Exblifep?

Exblifep is a combination antibiotic used for cUTIs that contains two antibiotics, cefepime and enmetazobactam. Exblifep is used when the bacteria causing the UTI is resistant to other antibiotics, especially if the resistance is due to Extended Spectrum Beta Lactamases (ESBLs). Exblifep contains cefepime (Maxipime), which is fourth-generation cephalosporin combined with enmetazobactam, which is a beta-lactamase inhibitor. Exblifep is given as an IV infusion that takes about 2 hours and is given every 8 hours for 7 to 14 days. Exblifep received FDA approval to treat adults (18 years and older) with complicated UTI, including kidney infection (pyelonephritis) caused by specific bacteria *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, and Enterobacter cloacae complex*, that are susceptible to Exblifep.

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Exblifep side effects:

- **Common side effects** are headache, infusion side effects including inflame mation of the vein (phlebitis), increased liver enzyme transaminases, and high bilirubin levels; these side effects occurred in 5% or more of patients using Exblifep.
- **Less common side effects** include diarrhea, anemia, hypersensitivity, vomiting, and nausea; these side effects occurred in less than 5% of patients using Exblifep.
- **Serious side effects**: Get emergency medical help if you have signs of an allergic reaction to this medicine: hives, difficulty breathing, swelling of your face, lips, tongue, or throat.
- **Other serious side effects** include neurotoxicity, diarrhea due to Clostridioides difficile, increased prothrombin time, and development of drug-resistant bacteria.

How will I receive Exblifep?

Exblifep is a solution given into your vein by a 2 hour intravenous (IV) infusion every 8 hours for 7 days and up to 14 days for patients with concurrent bacteremia.

Dosing information:

The recommended dose of Exblifep is 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) between 60 and 129 mL/min. Dose changes are required for varying degrees of renal function. For patients with changing renal function, monitor serum creatinine concentrations and eGFR at least daily and adjust the dosage accordingly. Exblifep 2.5 grams (cefepime and enmetazobactam) for injection contains 2 grams cefepime and 0.5 grams enmetazobactam as a sterile powder for reconstitution in single-dose vials.

Storage

⇒ **Vials:** Store vials refrigerated at 2°C to 8°C (36°F to 46°F); excursions are permitted to 15°C to 25°C (59°F to 77°F) Keep the vials in the outer carton to protect from light.

⇒ **Diluted solution:** Store the prepared diluted solution refrigerated at 2°C to 8° C (36°F to 46°F) for up to 4 hours prior to administration. The intravenous infusion administration of the diluted solution must be completed within 6 hours of dilution.

References:

- *Exblifep. Available at: https://www.drugs.com/exblifep.html. Accessed in Febreuary, 2024.*
- *FDA approves Allecra's EXBLIFEP for cUTI treatment. Available at: https://www.pharmaceutical-technology.com/news/fda-approves-allecra-exblifep/. Accessed in February, 2024.*

Ph. Marwa Elsayed, PGCPD. M.Sc. cand.

FDA warns of potentially lethal reaction to seizure medications

The US Food and Drug Administration (FDA) has issued a warning on the antiseizure medications levetiracetam and clobazam. The alert highlights the possibility of a rare but serious drug hypersensitivity reaction, if not detected and treated promptly. The FDA reports that this condition, known as drug reaction with eosinophilia and systemic symptoms (DRESS), may begin as a rash but can rapidly progress to cause organ damage, hospitalization, and mortality. Through March 2023, an examination of the medical literature and the FDA Adverse Event Reporting System (FAERS) yielded a total of 32 severe cases of DRESS across the globe, all of which were associated with levetiracetam.

There were three cases reported in the United States, while the remaining 29 occurred internationally. Patients were hospitalized and received medical treatment in all 32 instances; two patients unfortunately died because of their injuries. In cases involving levetiracetam, the median latency to onset of DRESS was 24 days; the range was 7 to 170 days. Rash (n=22), fever (n=20), eosinophilia (n=17), lymph node enlargement (n=9), and atypical lymphocytes (n=4) were among the signs and symptoms that were reported.

Twenty-two levetiracetam-associated cases of DRESS involved injury to one or more organs, including the liver, lungs, kidneys, and gallbladder. In 25 of the 29 cases for which information on treatment discontinuation was available, DRESS symptoms resolved when levetiracetam was discontinued. As for clobazam, a search of FAERS and the medical literature through July 2023 identified 10 serious cases of DRESS worldwide one in the US, and nine abroad. All 10 patients were hospitalized and received medical treatment. No deaths were reported. The median time to onset of clobazam-associated DRESS was 21.5 days (range, 7 to 103 days). The reported signs and symptoms included skin rash (n=10), fever (n=8), eosinophilia (n=7), facial swelling (n=7), leukocytosis (n=4), lymph node swelling (n=4), and leukopenia/ thrombocytopenia (n=1). In nine cases, there was injury to one or more organs, including the liver, kidneys, and gastrointestinal tract.

DRESS symptoms resolved in all 10 cases when treatment with clobazam was stopped. DRESS and other serious skin reactions reported with clobazam, a benzodiazepine, have not generally been associated with other benzodiazepines, the FDA notes.

As a consequence of these incidents, the FDA reported that warnings concerning the risk of DRESS will be added to the prescription information and patient medication guidelines for these medications. "Health care professionals should be aware that prompt recognition and early treatment is important for improving DRESS outcomes and decreasing mortality," the Food and Drug Administration (FDA) warned.

They point out that diagnosis might be challenging since early signs and symptoms, such as fever and enlarged lymph nodes, can occur without the presence of a rash. DRESS may occur 2 to 8 weeks after taking levetiracetam or clobazam. Symptoms and severity might vary dramatically. Other dangerous skin responses to be aware of include Stevens-Johnson syndrome and toxic epidermal necrolysis.

References:

- *FDA Warns of Potentially Lethal Reaction to Seizure Meds, (2023). Available at: https://www.medscape.com/viewarticle/998860?reg=1&icd=login_success_email_match_norm. Accessed in March, 2024.).*
- *FDA warns of rare but serious drug reaction to the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan) | FDA, (2023). Available at :https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-rare-serious-drug-reaction-antiseizure-medicines-levetiracetam-keppra-keppra-xr-elepsia-xr . Accessed in March, 2024.*

Ph. Mai Mousa, PharmD., M.Sc. PhD cand.

How cigarettes scramble your genetic code

Smoking is widely known to be harmful to human health, increasing the risk of lung cancer, cardiovascular disease, and other serious conditions. But what exactly is happening at the molecular level that makes smoking so dangerous? A key factor is the effect smoking has on our DNA.

DNA Damage from Carcinogens Tobacco smoke contains at least 60 potent chemical carcinogens that have the ability to cause DNA damage. Some of the major carcinogenic compounds in tobacco smoke include polycyclic aromatic hydrocarbons like benzopyrenes, nitrosamines, aromatic amines, aldehydes, and certain metals like cadmium.

These carcinogens can form DNA adducts, where they chemically bind to DNA and distort its structure. If not properly repaired, DNA adducts can lead to mutations when the cell replicates its DNA and passes on the errors to new cells. The accumulation of mutations over time dramatically increases the risk of cancer by disrupting critical genes that control cell growth and division.

In addition to causing DNA adducts directly, the carcinogens in tobacco smoke also generate reactive oxygen species that can damage DNA through oxidation. This oxidative stress can result in other types of DNA lesions like strand breaks, and base modifications like 8-oxoguanine. If left unrepaired, these lesions can also cause mutations or trigger cell death. Smoking not only causes DNA damage directly, but it also impairs the immune system's ability to repair that damage and eliminate mutated cells. Studies show smoking reduces the activity of alveolar macrophages, neutrophils, natural killer cells, and other key immune cells responsible for identifying and destroying precancerous and cancerous cells in the lungs.

By suppressing immune surveillance and DNA repair mechanisms, smoking allows DNA mutations to persist and accumulate over time. This eventually leads to the survival and proliferation of malignant cells that are the precursors to lung cancer and other smoking-related cancers.

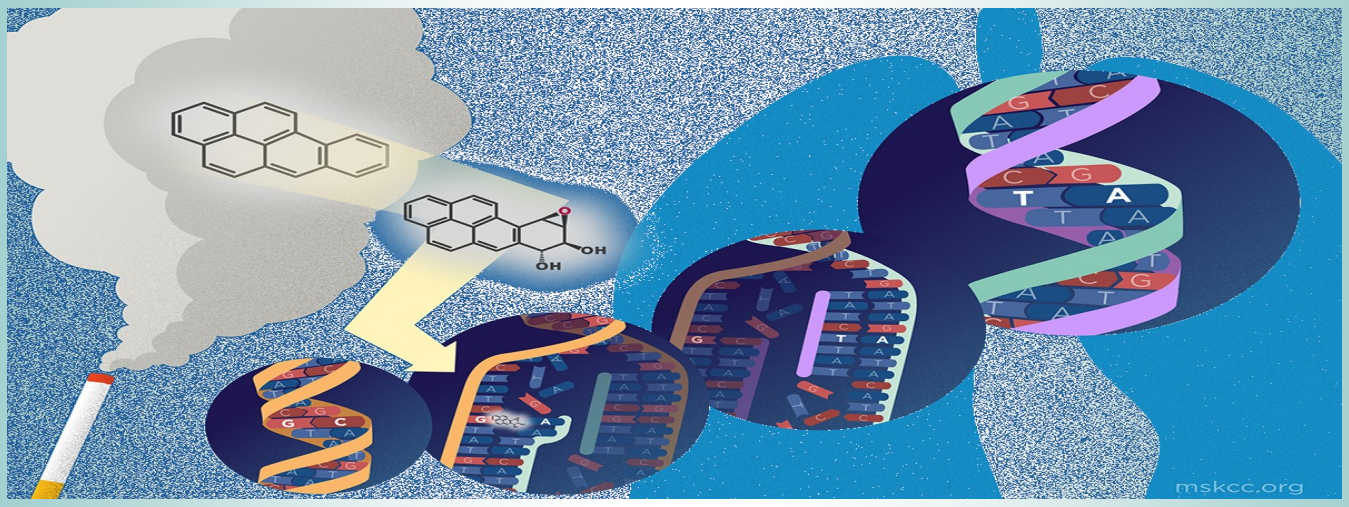
Nicotine's role even beyond the numerous carcinogens in tobacco smoke, the nicotine itself may contribute to the cancer process. Nicotine suppresses apoptosis (programmed cell death), which is a protective mechanism that removes cells with excessive DNA damage. This allows cells with mutations to survive when they would normally be eliminated.

Nicotine can also promote tumor growth by stimulating angiogenesis (new blood vessel formation) and upregulating growth factors that encourage rapid proliferation of the surviving mutated cells. So, while not a direct mutagen itself, nicotine creates a cellular environment conducive to the survival and spread of mutations caused by other components of tobacco smoke.

Mutational Signatures The molecular fingerprints of tobacco smoke can be seen in the patterns of mutations found in smoking-related cancers like lung cancer. Large genomic studies have identified specific mutational signatures associated with exposure to polycyclic aromatic hydrocarbons and other carcinogens in cigarette smoke.

These mutational signatures include a high prevalence of G>T transversions in tumor DNA, reflecting the types of guanine oxidation products and DNA adducts induced by the complex mixture of carcinogens in tobacco smoke. Smoking cessation remains one of the most effective ways to prevent these characteristic mutations from accumulating and causing cancer.

In summary, smoking is a major source of DNA damage through multiple mechanisms the introduction of carcinogenic DNA adducts and oxidative lesions, as well as the impairment of DNA repair and immunological defenses against mutated cells. By understanding smoking's mutagenic mode of action at the molecular level, we can better appreciate the grave genetic insults it inflicts and reinforce the importance of prevention and cessation efforts.



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- *Yamaguchi NH. Smoking, immunity, and DNA damage. Transl Lung Cancer Res. 2019;8(Suppl 1):S3-S6.*

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Phone: 040/3331577-3336007

Email: Tanta_DPIC@pharm.tanta.edu.eg

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Vision

The vision of Tanta University DPIC is to improve national healthcare service through provision of evidence-based, unbiased, patient oriented drug information services & adverse drug reporting system.

Mission

* Responding to drug inquiries related to the use of the drug and providing the health care professionals and patients with drug information related to the patient's care to achieve the optimal use of the drug in addition to the provision of other toxicological managing information.
* Educational activities to support the rational optimal use of drugs as well, supporting research activities.
* Continuous medical education and training courses in various fields of pharmacy for students, undergraduates, postgraduate students, and researchers.
* Issuing a Drug Information Bulletin periodically to take a look at medical & pharmaceutical news.
* Supporting the National Pharmaceutical Vigilance Program by following up and monitoring side effects and problems related to use of pharmaceutical preparations within regional hospitals.
* Contributing to the establishment of various treatment protocols and prescription booklet services in regional hospitals.

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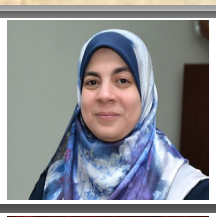

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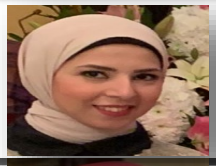

Reviewer:

Ph. Mai A. Mousa, PhrmD., M.Sc. PhD. Cand.

Editor:

Ph. Marwa E. Mohammed, PGCPD. M.Sc. Cand.