Drug & Poison Information Center—Faculty of Pharmacy—Tanta University

Drug & Poison Information Bulletin

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Post-marketing data lead to FDA-boxed warning to Tofacitinib

In this issue:

Tofacitinib is one of the Janus Associated kinase (JAK) inhibitors used to treat moderate to severe rheumatoid arthritis (RA) or active psoriatic arthritis in adults who have tried methotrexate or other medications without successful treatment of symptoms. Tofacitinib is sometimes given in combination with methotrexate or other arthritis medicines. It is also used to treat adults with moderate to severe ulcerative colitis. Extended-release tofacitinib is not for use in treating ulcerative colitis. The 10 mg twice daily dose of tofacitinib is not approved for RA or psoriatic arthritis. It's only approved for ulcerative colitis for initial treatment and for long-term use in limited situations.

Postmarketing safety study of tofacitinib at two doses (10 mg twice daily and 5 mg twice daily) in combination with methotrexate in comparison to tumor necrosis factor (TNF) inhibitor was conducted. During the study, an external data safety monitoring committee found an increased occurrence of pulmonary embolism (PE) and death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF inhibitor.

The US Food and Drug Administration (FDA) first warned about these risks in February 2019. In May, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) advised physicians not to prescribe the 10 mg twice daily dose of tofacitinib to patients at high risk for PE.

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While FDA warns that these increased risks in patients taking this dose for RA, these risks may also apply to those taking tofacitinib for ulcerative colitis. Recently, the FDA has added a boxed warning to tofacitinib noting an increased risk for PE and death with the higher dose of the drug. In addition, the agency has limited its use for ulcerative colitis to patients who are not treated adequately or who experience severe adverse effects with other drugs.

Recommendations:

Health care professionals should:

⇒ Follow the recommendations in the tofacitinib prescribing information for the specific condition they are treating.

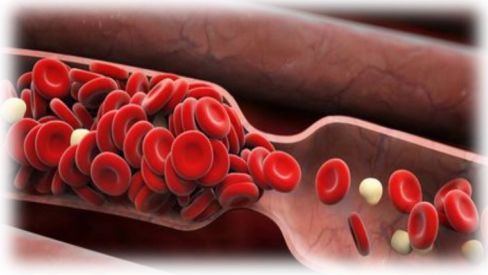
⇒ Monitor patients for the signs and symptoms of PE, and advise them to seek medical attention immediately if they experience them.

Patients should:

⇒ Not stop or change the dose of tofacitinib without first talking to health care professional, otherwise condition may get worse.

⇒ Seek medical attention immediately if experience symptoms of a blood clot in lungs or other unusual symptoms such as:

- *Sudden shortness of breath or difficulty breathing.*
- *Chest pain or pain in your back.*
- *Coughing up blood.*
- *Excessive sweating.*
- *Clammy or bluish colored skin.*



References:

- ***Megan Brooks. FDA Adds Boxed Warning on Risk for PE, Death With Higher Dose Tofacitinib (Xeljanz). https://www.medscape.com/viewarticle/916105. Accessed in July, 2019.***
- ***Tofacitinib. https://medlineplus.gov/druginfo/meds/a613025.html. Accessed in July, 2019.***

Ph/Bassant Maher, B.Sc

New drug approval for narcolepsy

The US Food and Drug Administration (FDA) has approved pitolisant (Wakix, Harmony Biosciences) August 14, 2019 for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy. Narcolepsy is a rare, long-term sleep disorder which affects the brain's ability to regulate the normal sleep-wake cycle. Narcolepsy is characterized by excessive daytime sleepiness, episodes of muscle weakness (cataplexy), hallucinations related to sleep, sleep paralysis, broken sleep at night, reduced attention span as well as non-sleep symptoms such as obesity, anxiety, and cognitive and emotional problems. Not all symptoms are present in all patients. The age of onset varies from early childhood to around 50 years.

Mechanism of action:

Pitolisant, a first-in-class medication, is a selective histamine 3 (H3) receptor antagonist/inverse agonist that works through a novel mechanism of action to increase the synthesis and release of histamine, a wake-promoting neurotransmitter in the brain. It is administered orally once daily in the morning upon waking.

Clinical data:

The efficacy of pitolisant was evaluated in two multicenter, randomized, double-blind, placebo-controlled studies involving 261 patients with narcolepsy with or without cataplexy. Treatment lasted 8 weeks, with a 3-week dose titration phase followed by a 5-week stable-dose phase. In both studies, pitolisant demonstrated a statistically significant improvement in EDS, as measured by the Epworth Sleepiness Scale score.

Safety issues:

The most common adverse reactions (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%). Pitolisant is contraindicated in patients with severe liver disease. The risk of QT prolongation may be greater in patients with liver or kidney disease and not recommended in patients with end-stage kidney disease.

References:

- *FDA Approves Wakix: https://www.drugs.com/newdrugs/fda-approves-wakix-pitolisant-first-class-excessive-daytime-sleepiness-adult-patients-narcolepsy-5030.html . Accessed in August, 2019.*
- *Search Orphan Drug Designations and Approvals: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=307210 . Accessed in August, 2019.*

By: Ph/Mai Mousa, PharmD

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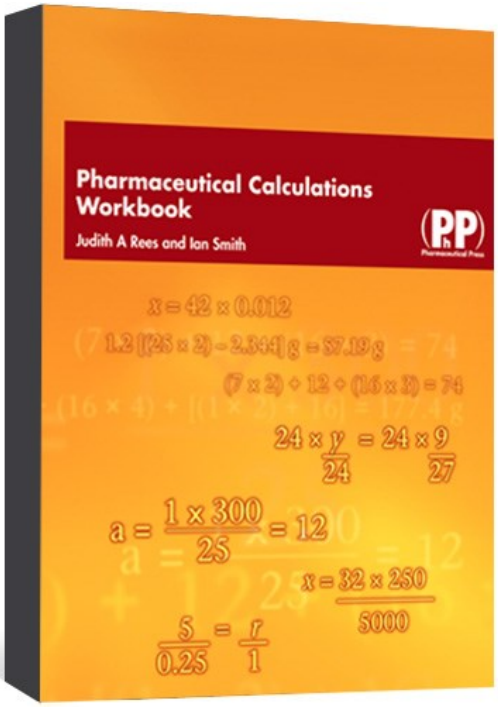
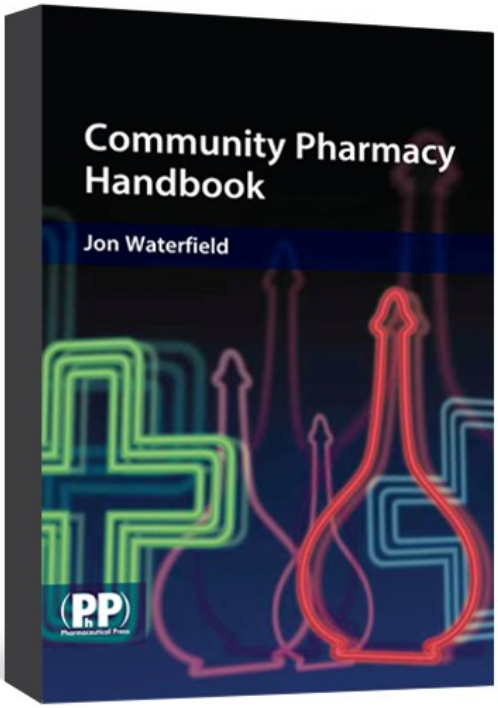
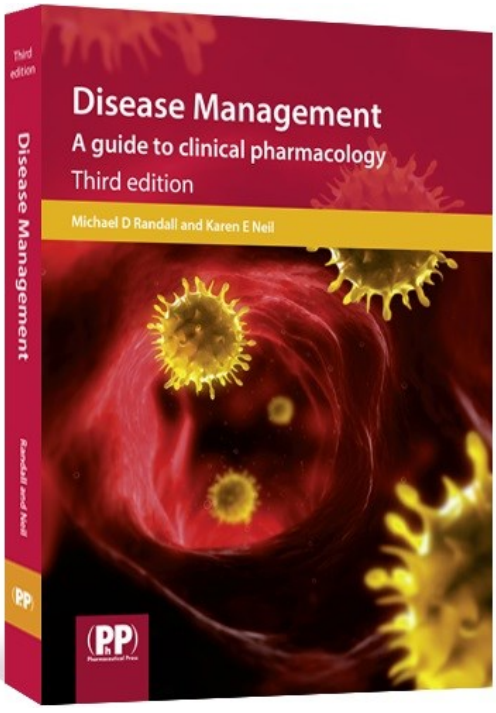




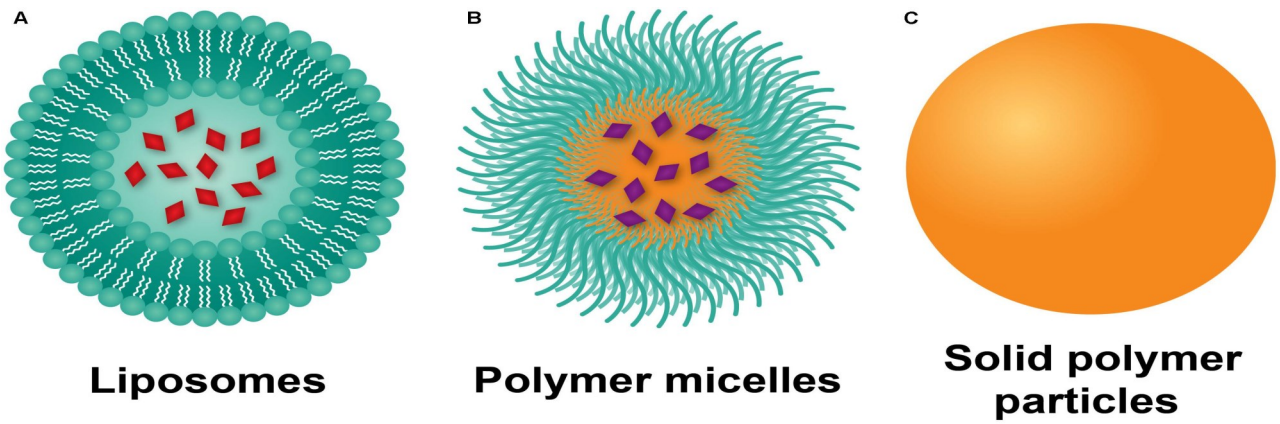


Nano-medicines in treatment of resistant hypertension.

Despite significant progress in pharmacological management of patients with primary hypertension, treatment-resistant hypertension (TRH) is still relatively prevalent among them. This condition is defined as blood pressure that remains above goal, despite concurrent use of optimal doses of 3 antihypertensive drugs of different classes and exclusion of secondary causes of hypertension.

Consequently, there is an urgent need to develop and test novel, safe, and efficacious drugs for RH to improve long-term clinical management and outcomes of patients. To date, about 50 nanodrugs have been approved by the Food and Drug Administration (FDA) for various indications predominantly cancer, infections, and bone substitute. However, although it is well established that marketed anti-hypertension medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium-channel blockers, have low oral bioavailability and potentially serious adverse effects, no nanodrugs are presently approved for cardiovascular disorders, including TRH.

In vivo studies highlight the potential for using previously FDA-approved anti-hypertensives with nanoparticle formulations to safely combat TRH. Fancher et al. reported the beneficial effects of nanomedicine in reducing blood pressure and improving bioavailability of standard anti-hypertensives and poorly soluble biomolecules (e.g., Superoxide dismutase (*SOD*)).



FDA-approved anti-hypertensives that show promising *In Vivo* results for treatment of hypertension when combined with nanoparticle(NP) formulations.

FDA-Approved Antihypertensive	NP Formultion	NP Deliery Method	In Vivo Model of Hypertension	Effect of NP-Antihypertensive on BP	Bioavailability
SOD	Liposome encapsula-tion	Daily injections (×8 d)	5-d infusion of Ang II in rats	Reduced MAP by 50 mm Hg	Increased circulation time of 5 h
Lercanidipine	Proliposome	Oral dose using intragastric tube	DOCA salt protocol, rats*	Immediate and long-lasting (24 h) reduction of SBP	t.=6.95 h (vs 5.26 h for free drug)
Felodipine	PLGA	Orally (1 mg/kg)	DOCA salt protocol, rats*	Long-lasting (4 d) reduction of SBP compared with free drug (<2 d)	Sustained release in vitro (144 h). In vivo measures NA
Aliskiren	Magnetic poly(D,L lactide)	Oral gavage	Spontaneously hypertensive rats	Reduced SBP ≈25 mm Hg compared with aliskiren alone	NA

Ang II indicates angiotensin II; BP, blood pressure; **DOCA**, deoxycorticosterone acetate; **FDA**, Food and Drug Administration; **MAP,** mean arterial pressure; **NA**, not available; **NP,** nanoparticle; **PLGA,** polylactide-co-glycolide; **SBP**, systolic blood pressure; **SOD,** superoxide dismutase; and t., half-life. ***Subcutaneous injections of DOCA in olive oil administered twice weekly for 4 wk. Doses varied from 20 to 25 mg/kg among studies.**

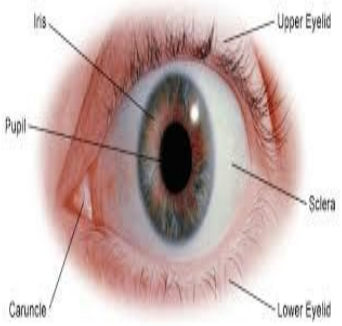
This approach improves formulations of poorly water-soluble, low-bioavailability, and unstable active pharmaceutical ingredients (APIs) , promote controlled drug release during an extended period of time, and enable targeted delivery of antihypertensive drugs to injured tissues thereby improving both safety and efficacy.

References:

- ***Fancher IS, Rubinstein I, Levitan I. Potential strategies to reduce blood pressure in treatment-resistant hypertension using Food and Drug Administration–approved nanodrug delivery platforms. Hypertension, 2019 ;73:250-257.***
- ***Muhlebach S. Regulatory challenges of nanomedicines and their follow- on versions: a generic or similar approach? Adv Drug Deliv Rev. 2018;131:122–131.***

By: Ph/ Marwa EL-Hefnawy, M.Sc.

In-situ gelling systems for eye drug products, an overview



Eye is the most sensitive organ of the body. Designing of ocular drug delivery system is the most challenging field for pharmaceutical scientists as less than 5% of administered drug enters the eye due to:

⇒ The complicated anatomical structure of the eye.

⇒ Small absorptive surface & low transparency of the cornea.

⇒ Lipophilicity of corneal epithelium.

⇒ Pre corneal loss (due to nasolacrimal drainage).

⇒ Blinking.

⇒ Low capacity of conjunctival sac, that restricts the entry of drug molecule at the site of action .

To improve ophthalmic drug bioavailability, there are considerable efforts directed towards newer drug delivery systems for ophthalmic administration.

In-situ gelling systems:

In situ gel forming systems are drug delivery systems that are in solution form before administration in the body but once administered, undergo gelation *in-situ*, to form a gel triggered by external stimulus such as temperature, pH etc. and release the drug in sustained or controlled manner. This novel concept of producing in situ gel was suggested for the first time in the early 1980s.

Advantages of *in-situ* gelling systems as ophthalmic products:

⇒ Less blurred vision as compared to ointment.

⇒ Sustained, prolonged drug release.

⇒ Reduced frequency of applications hence improved patient compliance.

⇒ Improved local bioavailability due to increased eye contact time.

Mechanisms of gel formation for *in-situ* gelling systems:

⇒ **Temperature-induced *in-situ* gel systems:** Gel formation occurs at 37°C.

⇒ **pH-induced *in-situ* gel systems:** Gel formation occurs in the pH range of the eye (7-7.4).

⇒ **Ion-activated systems :** Gel forms as a result of cross-linking with the cations ($Ca^{+,}$ K^{+}) present in the tear fluids.

Examples of some marketed *in-situ* gelling ophthalmic products:

⇒ ***Timoptic-XE®*** solution (Timolol maleate).

⇒ ***Azasite drops®*** (Azithromycin).

⇒ ***Aktin-TM®*** (Lidocaine hydrochloride).

⇒ ***Virgan gel®*** (Ganciclovir).

Refernces:

- *Yumei Wu, et al. Research progress of in-situ gelling ophthalmic drug delivery system. Asian Journal of Pharmaceutical Sciences 14 (2019) 1–15.*
- *Asmat Majeed and Nisar Ahmad Khan . Ocular in situ gel: An overview. Journal of Drug Delivery & Therapeutics. 2019; 9(1):337-347 .*

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