مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

Pharmacy Newsletter

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Ticagrelor (Brilinta®) Medication Utilization Evaluation (MUE) Results

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Introduction:

Ticagrelor is an antiplatelet agent that belongs to the oral $P2Y_{12}$ –receptor inhibitors which include clopidogrel and prasugrel as well. Ticagrelor is indicated to be used for reduction of the rate of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS.

Justification for the MUE:

Evaluate appropriate utilization of ticagrelor as 2nd line therapy for secondary prevention of major cardiovascular events, myocardial infarction (MI), and stroke in patients with acute coronary syndromes (ACS) or a history of MI.

Approved indication at KFSHRC:

Ticagrelor is approved as a 2nd line agent for clopidogrel non-responders, patients presenting to the emergency department for secondary prevention of thrombotic events in patients with ACS managed medically or undergoing percutaneous coronary intervention (PCI). Ticagrelor is given in conjunction with aspirin.

Formulary Restriction: Ticagrelor is restricted to Adult Cardiology and Emergency Physicians.

Dosage Form Available at KFSH&RC: Tablet: 90 mg

Formulary Alternatives: Clopidogrel 75 mg (Plavix®)

Methodology:

Study design: Retrospective MUE study (data collected from PowerChart and paper chart when needed).

Sample size: 49 patients

Inclusion criteria: All patients who received ticagrelor in 2015 (12 months).

Exclusion criteria: All patients who received ticagrelor before or after 2015.

Results:

Summary of MUE Results:

1. Number of patients who were prescribed ticagrelor in the year 2015 at KFSHRC was 49 patients, while the estimated number for patients who may need the drug as second line therapy was initially estimated to be 100-200 patients per year.
2. Among the 49 patients who were prescribed the drug, 35 (71.4%) met the approved indication as second line therapy, while 14 (28.6%) got the drug as first line therapy.
3. Among the 14 patients who received the medication as first line (unapproved indication), only 4 (28.6%) patients received the drug per physician prescription from KFSHR, while the rest 10 patients (71.2%) got ticagrelor from outside hospitals as initial first line therapy, and continued at KFSHRC.
4. About 96% of patients received ticagrelor for percutaneous coronary intervention management (PCI).
5. Among patients who received ticagrelor, initially at KFSHRC about 28% didn't receive a loading does and 97% received an appropriate maintenance dose.
6. Duration of treatment with ticagrelor post PCI was appropriate as recommended in the AHA guidelines, drug-eluting stent (DES) at least 12 months is patient has no risk of morbidity from bleeding, and for bare-metal stent (BMS) at least 1 month, among 41 (83.7%) patients .

In this issue

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Formulary & Therapeutics Committee Updates

The following are formulary changes by the Formulary & Therapeutics Committee (FTC) from Apr-Jun 2018 meetings. Please refer to the Online Hospital Formulary to check the status of the new medications and details on dosing and uses.

Approved New Formulary Addition

- **Carglumic Acid (Carbaglu®) 200 mg Tablet**

  Treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) in adults and pediatrics. Prescribing is restricted to medical genetics consultants/assistant consultants and fellows.

- **Sodium Phenylbutyrate Powder for Oral Solution**

  Treatment of hyperammonemia in patients with urea cycle disorder. Prescribing is restricted to medical genetics consultants/assistant consultants and fellows. Requires submission of an indication form as per the approved guidelines.

- **Glucarpidase (Voraxaze®) 1000 IU Vial, Intravenous Injection**

  Treatment of toxic methotrexate plasma concentrations (>1 micromole/L) in patients with delayed clearance due to renal impairment. Prescribing restricted to adult and pediatric hematologists and oncologists as per guidelines.

- **Ponatinib (Iclusig®) 15 mg Tablet**

  Treatment of CML in chronic, accelerated or blast phase in patients for whom no other tyrosine kinase inhibitor therapy is indicated or who are T315I-positive, and for the treatment of Ph+ALL in patients for whom no other tyrosine kinase inhibitor therapy is indicated or who are T315I-positive. Prescribing is restricted to adult hematologists. as per guidelines.

Approved New Dosage Form Addition

- **8-Methoxypsoralen 10 mg Tablet**

  This dosage form will completely replace the 10 mg oil-filled capsule. Refer to the online formulary for approved indications.

Approved Formulary Deletion

- **8-Methoxypsoralen 10 mg Oil-filled Capsule**

  Replaced by tablet dosage form.

Approved Guidelines

- **Azoles Therapeutic Drug Monitoring Guideline**

  To optimize drug therapy of azole antifungals and assure efficacy and safety following therapeutic drug levels.

- **Rituximab IV/SC Prescribing Guidelines for Oncology and Hematology Disorders in Adult Patients**

  Updated guidelines to incorporate the recently approved subcutaneous formulation.

- **Colistimethate Sodium (Colistin®) Dosing Guidelines**

  Updated pediatric dosing and adult CRRT dosing.

Approved Miscellaneous

- **New Regulations for Pregabalin (Lyrica®)**

  Formulary restrictions changed to be a controlled medication according to the new SFDA regulations. Accordingly, its prescribing will be according to the prescribing restrictions for controlled medications as per the General Narcotics and Controlled Medication Policy [MCO-CS-PCM-07-001].

- **Antimicrobial Prophylaxis for Lung Transplant Protocol**

For more information on the indications, age specifications, doses and guidelines please check the online hospital formulary: http://online.lexi.com/lco/action/home

FTC Updates *Contd...*

New Azole Therapeutic Drug Monitoring (TDM) Guideline

The guideline offers new guidance on therapeutic drug monitoring of azole antifungals to ensure safety on prescribing. Routine monitoring of azole antifungals is generally not required. However, the indications for therapeutic drug monitoring are appropriate when there is questionable compliance, issues with gastrointestinal absorption, drug interactions and suspected toxicity. The guideline features:

- Formulary azole antifungals: Itraconazole, Posaconazole and Voriconazole
- Guidance on timing of when trough levels should be drawn with first dose, including specific recommendations based on duration of therapy and dosage form e.g. delayed release tablet, oral suspension
- Tables to distinguish target therapeutic levels in both treatment and prophylaxis dosing
- Serum trough concentration-range recommendations based on dosage form, type of infection and response to management e.g. poor responders
- Dose adjustment recommendations in both treatment and prophylaxis management based on therapeutic serum concentration range
- Therapeutic concentration ranges indicating toxicity, signs of toxicity and dose adjustments in toxicity
- Subsequent serum trough concentration monitoring illustrates when to repeat levels based on duration of therapy or last dose adjustment
- Monitoring parameters such as hepatic function as azoles are metabolized by the liver, at baseline and once weekly, ECG (QTc interval), vision and neurological signs
- If the patient is on other QTc prolonging medications and/or QTc is prolonged at baseline, ECG monitoring is recommended. For more information refer to the *Drug Induced QTc Prolongation Monitoring Guideline for Hospitalized Patients* link: https://www.kfshrc.edu.sa/store/media/5q8.pdf
- To access the *Azole TDM Guideline* refer to the online hospital formulary or FTC medication guidelines link: https://www.kfshrc.edu.sa/store/media/8m6.pdf

Ministry of Health Hajj Vaccination Requirements

1. Meningococcal meningitis tetravalent (ACYW135) conjugate vaccine
2. Seasonal influenza vaccine

Note: Both vaccines should be administered at least 10 days prior to commencing hajj.

What is in the News

US-FDA Highlights Risk of Rare and Severe Immune reaction Hemophagocytic Lymphohistiocytosis (HLH) with Lamotrigine (Lamictal®)

A safety warning has been added to lamotrigine's label on the risk of a rare but very severe immune reaction called Hemophagocytic Lymphohistiocytosis (HLH) that can result in hospitalization and death.

Signs and symptoms of HLH include but are not limited to fever (> 38 °C), hepatomegaly, lymphadenopathy, skin rashes, jaundice, unusual bleeding and symptoms involving the nervous system. HLH can occur within days to weeks after starting treatment.

Diagnosis of HLH is established by the presence of five out of the eight following signs or symptoms: fever and rash, splenomegaly, cytopenias, low blood fibrinogen or hypertriglyceridemia, elevated blood ferritin, hemophagocytosis identified by biopsy (bone marrow, spleen, or lymph node), decreased or absence of natural killer cell activity and elevated levels of CD25.

If these symptoms occur, treatment with lamotrigine should be discontinued if no alternative etiology is established. Healthcare providers should promptly evaluate all patients who develop fever or rash and discontinue lamotrigine if HLH is suspected, with no alternative reason for signs and symptoms is established.

Patients on lamotrigine are advised to seek immediate medical attention if they experience any symptoms of HLH.

US-FDA Report Serious Cases of Neural Tube Birth Defects in Infants of Pregnant Women taking Dolutegravir

The U.S. Food and Drug Administration (FDA) released a safety communication in regards to serious cases of neural tube birth defects involving the brain, spine, and spinal cord reported in babies born to women treated with dolutegravir.

Preliminary results from an ongoing observational study found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester, appear to be at higher risk for these defects. To date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir in later stages of pregnancy.

Health care professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy.

Additionally, health care professionals should consider:

- If dolutegravir is used in women of childbearing potential, the use of effective birth control should be consistently reinenforced
- Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing potential to exclude pregnancy

US-FDA Update Label Warnings on effect of Fluoroquinolone Antibiotics on Blood Sugar Levels and Mental Health

The U.S. Food and Drug Administration (FDA) is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood glucose and certain mental health side effects.

The mental health side effects to be added to or updated across all the fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium. This affects only the fluoroquinolone formulations taken by mouth or given by injection.

Changes to the drug labels have been made for all the fluoroquinolone group due to a recent review of life-threatening reports of low blood glucose side effects and additional mental health side effects.

Despite both low and high effects on blood glucose are well known and documented with the use of fluoroquinolones, the label has now been updated to include hypoglycemia that can lead to coma.

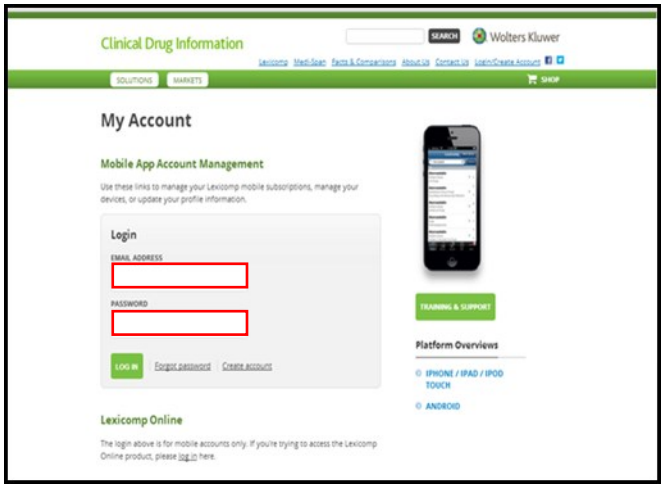
The FDA is investigating this new safety issue and will release an update as more information will be available.

All drug safety alerts are communicated to the end-users of concern, as per the IPP MCO-CS-PCS-07-075: Dissemination and Action Related to Drug Safety Alerts at KFSHRC. For more info access IPP via Unified KFSH&RC Portal.

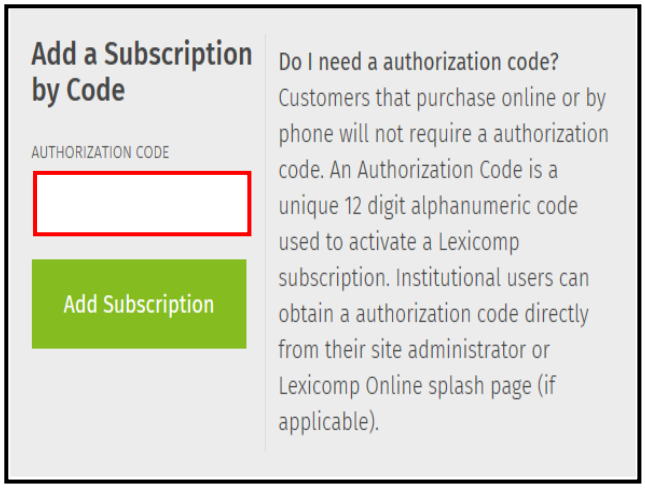
Tip of the Issue

Formulary Access on your Handheld Device

1 For new users visit the Lexicomp website: https://www.lexi.com/account/ to register a new account or sign in as an existing user

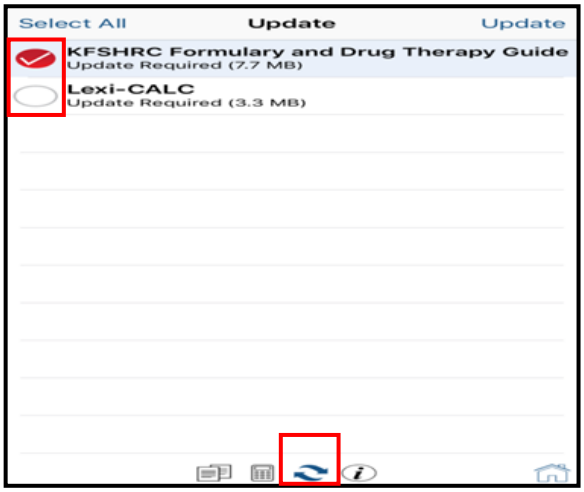


2 Enter the individualized subscription code sent on request from the Drug Information Center



3 Download the Lexicomp application on your smartphone and sign in to the application to synchronize with your personal account

4 Select KFSHRC Formulary and Drug Therapy Guide and click the update button at the bottom of the application page



You are now ready to access the hospital formulary from your smartphone

KFSHRC hospital staff (Riyadh) can email a request for smartphone access to the KFSHRC Formulary to: druginformationcenter@kfshrc.edu.sa

Pharmacy Newsletter

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Brilinta® MUE Report *Continued…*

7. Among patients who received ticagrelor, 7 (14.3%) patients developed adverse drug reactions.
8. Ticagrelor was discontinued in 20 (40.8%) of the patients.
9. From those 20 patients who discontinued ticagrelor 12 (24.5%) patients where switched back to clopidogrel.

Recommended Action Plan:

1. Share the result with King Faisal Heart Institute (KFHI).
2. Discuss the use of ticagrelor as first line therapy for patients who are at high risk category and who does not have high bleeding risk or any contraindication to ticagrelor.
3. Encourage reporting ADR's related to ticagrelor.

Table I: Patients Demographics:

Gender	Number of Patients
Male	40 (81.6%)
Female	9 (18.4%)
Mean Age	58 years

Table II: Anticoagulation or Antiplatelet Therapy prior to Ticagrelor Initiation:

Therapy prior to Ticagrelor initiation	Number of Patients
Yes	44 (89.8%)
i. Aspirin only	8 (16.3%)
i. Clopidogrel only	1 (2%)
i. Aspirin and clopidogrel	34 (69.4%)
i. Rivaroxaban, aspirin and clopidogrel	1 (2%)
None	5 (10.2%)

Table III: Anticoagulant or Antiplatelet Discontinuation Agents prior to Ticagrelor Initiation:

Medication	Number of Patients
Discontinued anticoagulant or antiplatelet therapy prior to ticagrelor initiation (i.e. clopidogrel)	35 (71.4%)
Continued anticoagulant or antiplatelet therapy prior to ticagrelor initiation	14 (28.6%)

Table IV: Concurrent Anticoagulant or Antiplatelet Therapy:

Concurrent Medication	Number of Patients
Aspirin only	48 (98%)
Aspirin and clopidogrel plus ticagrelor	1 (2%)
Aspirin dose with ticagrelor	
i. 81 mg = appropriate dose	48 (98%)
ii. 162 mg	1 (2%)

Table V: Indications for Ticagrelor:

Indication	Number of Patients
PCI:	
i. BMS	1 (2%)
ii. DES	47 (95.9%)
Patients enrolled in clinical trial	1 (2%)

Table VI: Ticagrelor Dose:

Dose	Number of Patients
Appropriateness of loading dose (180 mg once) in patients initiated at KFSHRC	**n= 36**
Appropriate dose	22 (61%)
Inappropriate dose (not given)	10 (28%)
Not documented	4 (11%)
Appropriateness of maintenance dose (90 mg BID)	**n= 47**
Appropriate dose	46 (97.9%)
Inappropriate dose	
i. Wrong dose (90 mg QD)	1 (2.1%)

Table VII: Duration of Ticagrelor:

Duration	Number of Patients
< 3 months	8 (16.3%)
≥ 6 months	8 (16.3%)
≥ 12 months	33 (67.3%)
Duration appropriateness	
i. Appropriate duration	41 (83.7%)
ii. Inappropriate duration	8 (16.3%)

Table VIII: Adverse Drug Reactions (ADRs):

ADR	Number of Patients
Bleeding	3 (6.1%)
Dyspnea	4 (8.2%)
Other (ventricular pause)	1 (2%)
Total number of ADRs	**7 (14.3%)**

Table IX: Ticagrelor Discontinuation:

Reasons for Discontinuation	Number of Patients
Due to ADR	5 (10.2%)
Loss of follow up	4 (8.2%)
Physician decision	7 (14.3%)
Ticagrelor failure (stent stenosis)	1 (2%)
Heart transplant	1 (2%)
Completed duration of therapy	2 (4%)
Switched back to clopidogrel	12 (24.5%)
Total number of ticagrelor discontinuation	**20 (40.8%)**

References available on request