In May 2011, the oral direct factor Xa inhibitor **Apixaban** (ELIQUIS) has been approved by the European Commission for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, and this is the first approval of the drug worldwide. (1)

**Apixaban** is one of the **novel oral anticoagulants**, including the other factor Xa inhibitor, Rivaroxaban (XARELTO) and the direct thrombin inhibitor Dabigatran (PRADAXA). **Apixaban and Rivaroxaban have shown superiority to Enoxaparin**, while Dabigatran has much larger indication for stroke prevention in atrial-fibrillation patients and approved for this indication in the US and Canada. (2)
Apixaban VS Enoxaparin (2, 3)

The Apixaban clinical program was designed to demonstrate the efficacy and safety of Apixaban for the prevention of VTE in a broad range of adult patients undergoing elective hip or knee replacement. The Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 3 (ADVANCE-3) trial, published in The New England Journal of Medicine, showed that Apixaban was statistically superior to Enoxaparin in reducing the incidence of venous thromboembolism in patients undergoing elective total hip replacement surgery. ADVANCE-2 study included patients undergoing elective knee replacement. Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal DVT, non-fatal pulmonary embolism (PE), and VTE-related death, compared to Enoxaparin in both elective hip and knee replacement surgery.

In the knee replacement surgery study during the intended treatment period, in the Apixaban arm 4 cases of PE were diagnosed against no cases in the Enoxaparin arm. No explanation can be given to this higher number of PE.

Apixaban VS Aspirin

The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study was designed to determine the efficacy and safety of Apixaban, at a dose of 5 mg twice daily, as compared to aspirin, at a dose of 81 to 324 mg daily, for the treatment of patients with atrial fibrillation for whom vitamin K antagonist therapy was considered unsuitable.

To evaluate the net benefit of Apixaban, a composite outcome of ischemic events and major bleeding is included. The rate of this outcome was significantly reduced with Apixaban as compared to aspirin (4).

Apixaban VS Warfarin …the Latest updates

Atrial fibrillation (AF) is associated with increased risk of stroke and can be attenuated with vitamin K antagonists. However, their use is limited due to high incidence of complications when patients' international normalized ratios (INRs) deviate from the target range. The primary
objective of ARISTOTLE (Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation) is to determine if Apixaban is non-inferior to Warfarin at reducing the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism in patients with AF and at least one additional risk factor for stroke. The key secondary objectives were to determine whether Apixaban is superior to Warfarin for the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism, and for all-cause death. (5) ARISTOTLE enrolled over 18,000 AF patients in more than 1000 centers in roughly 40 countries, and the trial randomized patients to either a twice-daily dose of Apixaban 5 mg or dose-adjusted Warfarin. (2)

In June 2011, top line results from the ARISTOTLE trial suggested that Apixaban is non-inferior to the older standard for the prevention of stroke and systemic embolism. According to preliminary results of the study, released lately, Apixaban also met the key secondary end points of superiority on efficacy and on ISTH (International Society on Thrombosis and Haemostasis) major bleeding compared with Warfarin. Full results of the trial will be presented August 28 at the European Society of Cardiology 2011 meeting in Paris, France. (2)

If ultimately approved, Apixaban would compete in this indication against Dabigatran, which is already on the US and other markets, as well as Rivaroxaban, still waiting for US approval. (2)

About Apixaban (6)

- **Mechanism of action:** Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It doesn’t require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot bound factor Xa and prothrombinase activity. It has no direct effects on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin.

- **Apixaban dosage:** The recommended dose of Apixaban (Eliquis) is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery. Switching treatment from parenteral anticoagulants to Apixaban (and vice versa) can be done at the next scheduled dose.

  **In patients undergoing hip replacement surgery:**
  The recommended duration of treatment is 32 to 38 days.

  **In patients undergoing knee replacement surgery:**
  The recommended duration of treatment is 10 to 14 days.
Apixaban and renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment. It should be used with caution in patients with severe renal impairment. It is not recommended in patients with creatinine clearance < 15 ml/min or in patients under going dialysis.

Apixaban and hepatic impairment: Apixaban is contraindicated in patients with hepatic coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment but no dose adjustment is required in these patients till now. Apixaban should be used cautiously in Patients with elevated liver enzymes, and ALT should be measured as part of the standard pre-operative evaluation.

Pediatric population: The safety and efficacy of Apixaban in children below age 18 haven’t been established.

Pregnancy and lactation: Apixaban is not recommended during pregnancy. A risk to newborns and infants cannot be excluded. A decision must be made to either discontinue breast-feeding or to discontinue Apixaban therapy.

Apixaban adverse effects: As with other anticoagulants, bleeding may occur during Apixaban therapy in the presence of associated risk factors. Common adverse effects are anemia, hemorrhage, contusion and nausea.

Overdose: There is no antidote to ELIQUIS. Overdose of Apixaban may result in a higher risk of bleeding. In the event of hemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g. surgical hemostasis or the transfusion of fresh frozen plasma should be considered. Activated charcoal may be considered in the management of Apixaban overdose. If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving Apixaban.

Information about excipients: ELIQUIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Hip fracture surgery: Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, it is not recommended in these patients.
Special warnings:

Hemorrhage risk

As with other anticoagulants, patients taking ELIQUIS are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of hemorrhage.

Interaction with other medicinal products affecting hemostasis

Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. Other platelet aggregation inhibitors or other antithrombotic agents are not recommended concomitantly with ELIQUIS.

Spinal/epidural anesthesia or puncture

Patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma when neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed. This risk may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of ELIQUIS. Patients are to be frequently monitored for signs and symptoms of neurological impairment.

There is no clinical experience with the use of Apixaban with indwelling intrathecal or epidural catheters. In case there is such need and based on PK data, a time interval of 20-30 hours (i.e. 2 x half-life) between the last dose of Apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of Apixaban may be given at least 5 hours after catheter removal. As with all new anticoagulant drugs, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using Apixaban in the presence of neuraxial blockade.

References:

2) The heart.org

March 3, 2011


6) European Medicines agency (EMEA)

MODIFIED DOSING RECOMMENDATION: ERYTHROPOIESIS-STIMULATING AGENTS (ESAs) IN CHRONIC KIDNEY DISEASE

June 24, 2011

“Epoetin alfa (marketed as Eprex) or Darbepoetin alfa”

ESAs treat certain types of anemia by stimulating the bone marrow to produce red blood cells and by decreasing the need for blood transfusions. FDA has modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population.

The new dosing recommendations are based on clinical trials showing that using ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke. Healthcare professionals should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions in CKD patients against the increased risks for serious cardiovascular events. Therapy should be individualized to the patient and the lowest possible ESA dose given to reduce the need for transfusions. (1)

Reference: 1-www.FDA.gov
VALPROATE PRODUCTS: RISK OF IMPAIRED COGNITIVE DEVELOPMENT IN CHILDREN EXPOSED IN UTERO (DURING PREGNANCY)

June 30, 2011

“Including Valproate sodium, Divalproex sodium, Valproic acid (Depakine), and their generics”

FDA notified healthcare professionals that children born to mothers who take the anti-seizure medication Valproate sodium or related products (Valproic acid and Divalproex sodium) during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. This conclusion is based on the results of epidemiologic studies that show that children born to mothers who took Valproate sodium or related products throughout their pregnancy tend to score lower on cognitive tests (IQ and other tests) than children born to mothers who took other anti-seizure medications during pregnancy.

Healthcare professionals should inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal Valproate exposure, and should continue to counsel women of childbearing potential taking Valproate about the increased risk of major malformations, including neural tube defects, when Valproate is used during pregnancy. In addition, healthcare professionals should weigh the benefits and risks of Valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. Alternative medications that have a lower risk of adverse birth outcomes should be considered. Patients should not stop taking Valproate without talking to a healthcare professional.\(^{(1)}\)

Reference: 1-www.FDA.gov

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From our answered questions

**Question 1:** What is the ability of switching Solucortef (hydrocortisone) to Dexamethasone (Decadron)?
The effects of different corticosteroids vary qualitatively as well as quantitatively, and it may not be possible to substitute one for another in equal therapeutic amounts without provoking adverse effects. For example Dexamethasone can’t be used for adrenocortical insufficiency for which hydrocortisone with supplementary Fludrocortisone is preferred.

✓ As a rough guide, the approximate equivalent doses of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties alone, are (1):
- Dexamethasone 0.75 mg
- Hydrocortisone 20 mg
✓ This table shows the comparison between hydrocortisone and Dexamethasone (2, 3):

<table>
<thead>
<tr>
<th></th>
<th>Hydrocortisone</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent potency dose (mg)</td>
<td>20</td>
<td>0.75</td>
</tr>
<tr>
<td>Half-life plasma (min)</td>
<td>80 to 118</td>
<td>110 to 210</td>
</tr>
<tr>
<td></td>
<td>Short-acting</td>
<td>Long-acting</td>
</tr>
<tr>
<td>Anti-inflammatory potency</td>
<td>1</td>
<td>20-30</td>
</tr>
<tr>
<td>Sodium-retaining potency</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

References:
2. Drug Facts and Comparisons, Basic and clinical pharmacology 13th edition (Katzung)

Question 2: What is the dose of Acetylcysteine as an antidote for Acetaminophen?

- **Acetylcysteine** is indicated as an **antidote** to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of **Acetaminophen**. It is essential to initiate treatment as soon as possible after the overdose and, in any case, within 24 hours of ingestion. (1)
- **Acetylcysteine** is reported to be most effective when administered within 8 hours of **Acetaminophen** over dosage, with the protective effect diminishing after this time. However, starting treatment with **Acetylcysteine** later (up to and beyond 24 hours) may still be of benefit. (3)
✓ **Only the 72-hour oral and 21-hour I.V. regimens are FDA-approved.** (2)

✓ **If given intravenously:** (1, 2, 3) 21-hour regimen: Consists of 3 doses; total dose delivered: 300 mg/kg:

1. **150 mg/kg** of Acetylcysteine in **200 mL of glucose 5%** is given initially over 15 minutes (UK) or over 60 minutes (USA), followed by infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one liter of glucose 5% over the next 16 hours.

2. Sodium chloride 0.9% may be used where glucose 5% is unsuitable.

3. The volume of intravenous fluids should be modified for children.

4. The fluid volume should be reduced in patients weighing <40 kg.

✓ **If given orally:** (1, 2, 3) **72-hour regimen:** An initial dose of **140 mg/kg** and is followed by **70 mg/kg** every 4 hours for an additional 17 doses, repeat dose if emesis occurs within 1 hour of administration.

**References:**

1. www.drugs.com
2. Lexicomp online
3. Martindale 35

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**Ketoconazole Withdrawal**

On 16/06/2011 the Egyptian Technical Committee (TC) at the Central Administration of Pharmaceutical Affairs (CAPA) has decided to withdraw the marketing authorization of the pharmaceutical products containing ketoconazole taken by the oral Route.

It is worth mentioning that the previous decision **is applied only on the oral route of ketoconazole 200 mg tablets and not** on the other dosage forms of Ketoconazole (e.g. topical forms & shampoo). (1)

This action was based on the French regulatory authority decision taken on 08/06/2011 to suspend its marketing authorization in the treatment of fungal infections, due to its risk of developing chronic liver disease and cirrhosis, more frequently and severely than with other antifungal treatments. (2)
It is worth mentioning that The French Agency for the Safety of Health Products (Afssaps) has recommended that, due to the availability of this drug in other European countries, proceedings for European reassessment of the benefit / risk of NIZORAL should be carried on by these countries. The outcome of this revaluation is still pending (3).

Ketoconazole used systemically -in particular- seems the only antifungal associated with a risk of developing chronic liver disease and cirrhosis, the use of topical medicines containing ketoconazole remains possible, due to the very low pass into the bloodstream and the absence of reports of liver toxicity with this route of administration.

The above decision includes the following brands: (Nizoral®, Conazole®, Fungizole®, Ketozele®& Kizol®) 200 mg tablets (1)

References:
1- www.ems.org.eg/akhpar_hama/newsletter
2- The French regulatory authority Article
3- The Afssaps. click here

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**Zinc Lozenges and Cold Symptoms**

High-dose, but not low-dose, zinc lozenges shorten the duration of common cold, according to the results of a meta-analysis reported in the July issue of *The Open Respiratory Medicine Journal*. The therapeutic effect of zinc lozenges on the duration of common cold episodes of natural origin was evaluated. Total daily zinc dose of less than 75 mg had no effect on common cold duration, whereas pooled data from 3 trials using zinc acetate in daily doses exceeding 75 mg showed a 42% reduction in the duration of colds. Zinc salts other than acetate in daily doses exceeding 75 mg, showed a 20% reduction in the duration of cold.

Zinc lozenges have caused adverse effects, such as bad taste, but there is no evidence that they would cause long term harm. The effects of zinc lozenges should be further studied to determine the optimal lozenge compositions and treatment strategies.
“Zinc lozenges available in the Egyptian market as Citra (Zinc gluconate 34.84 mg and Vitamin C 100 mg)”

References:

1) Medscape Pharmacists

Our Vision

The pharmacist working in Kasr Alainy Drug Information Center (KDIC) provides accurate, unbiased, relevant, evidenced based and timely information about drugs and drug related problems to assist the center users in optimizing health outcomes.

Our Mission

Pharmacists in the KDIC are part of the health care team working through the Clinical Pharmacology and Pharmacy committee, to provide useful service and the pharmaceutical information needed for the hospitals’ patients.

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