Part I of II

EPVC Newsletter

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Egyptian Pharmaceutical Vigilance Center (EPVC)

Pharmacovigilance Department

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The second conference for Arab FDA-Sharm El Sheikh

At the interval from 11 to 13 April 2015, the second Arab conference For Food and Drugs (Arab FDA) was held at Sharm El-Sheikh city.

This conference was under the supervision of the Prime Minister of Egypt, Eng. /Ibrahim Mahlab, and was attended by 500 participants representing 19 Arab countries & 6 foreign countries.

The conference is intended to be held periodically and the next conference is planned to be on 2017.

The recommendations of conference (regarding drugs):

1. Development of the Registration systems in the Arab countries.
2. Establishment of an organization to harmonize the pharmaceutical legislations to be a nucleus for the Arab drug Registration Authority.
3. Activation of the E-CTD system.
4. Investment in training of drug factories Inspectors and ensuring GMP implementation.
5. Exchange information between the members of the drug authorities at the Arab countries.
6. Enforcement of the Post Marketing Surveillance (PMS), activation of the Pharmacovigilance Centers and training of the staff.
7. Encourage the Arab countries to apply the clinical trials protocols and code of ethics and monitor its application.
8. The importance of development of the registration systems in the Arab countries and training the personnel to ensure the safety and efficacy of the pharmaceutical products.

9. The co-ordination between customs departments to overcome drugs counterfeit and violators should be punished.
10. Encourage the Arab countries to apply Bio-equivalence studies and ensure their adherence to the Good clinical practice (GCP).

EPVC – RMP training workshop in Cairo

The Egyptian Pharmaceutical Vigilance center (EPVC) has organized a training workshop on the New Arab Guidelines for RMP (Risk Management Plan) which was held at Hilton Ramses- Cairo.

50 Marketing Authorization Holders from all Arab countries has attended this training from 26th to 28th of April 2015.

Direct Healthcare Professional Communications (DHPC) and Safety label Changes - Serious slowing of the heart rate when amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug

On 5th April 2015, Egyptian Pharmacovigilance Center approved the distribution of DHPC concerning "warning of serious Symptomatic Bradycardia" when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing Sofosbuvir in Fixed dose combinations / Combinations with another Direct Acting Antiviral drug for example (but not restricted to) Ledipasvir, Daclatasvir or Simeprevir respectively. I

In addition to that MAH are requested to add the safety information about **the serious risk of bradycardia** to the SPC of their product in Egypt.

15 MAH in Egypt were communicated, 7 of which were granted the approval on the DHPC.

This warning was based on the FDA announcement.

Harvoni and Sovaldi are used to treat chronic hepatitis C, a viral infection that can last a lifetime

and lead to serious liver problems, including cirrhosis or liver cancer. These drugs reduce the amount of hepatitis C virus in the body by preventing the virus from multiplying within the body.

Additional Information for Health Care Professionals

- Postmarketing cases of serious and lifthreatening symptomatic bradycardia, as well as one

fatal cardiac arrest and cases requiring pacemaker insertion, have been reported when amiodarone is given with either Harvoni (a fixed dose combination with ledipasvir/ sofosbuvir) or Sovaldi (sofosbuvir) combined with another hepatitis C drug, such as daclatasvir, an investigational direct acting antiviral, or Olysio (simeprevir). Bradycardia may occur within the first few hours to days of initiating hepatitis C treatment, but cases have been observed up to 2 weeks after initiating treatment.

- The mechanism for this bradycardia effect is unknown.
- Harvoni should not be co-administered with amiodarone.
- Sovaldi (sofosbuvir) combined with another hepatitis C drug, such as investigational drug daclatasvir or Olysio (simeprevir), should not be co-administered with amiodarone.
- Similar cases of symptomatic bradycardia have not been reported in patients receiving Sovaldi with ribavirin or with pegylated interferon and ribavirin.
- Tell your patients to seek medical attention immediately if they have signs and symptoms of symptomatic bradycardia including:
    - Near-fainting or fainting (syncope)
    - Dizziness or lightheadedness
    - Malaise
    - Weakness
    - Excessive tiredness
    - Shortness of breath
    - Chest pains
    - Confusion or memory problems
- For patients taking amiodarone who have no other alternative treatment options and who will be co-administered either Harvoni or Sovaldi in combination with another direct-acting antiviral:
    - Counsel patients about the risk of serious symptomatic bradycardia
    - Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment
- Patients who are taking either Harvoni or Sovaldi in combination with another direct acting antiviral, who need to start amiodarone therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.
- Due to the long half-life of amiodarone, patients discontinuing amiodarone just prior to starting Harvoni, or Sovaldi in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.
- Encourage patients to read the patient information leaflet they receive with their prescription hepatitis C drugs and amiodarone as there may be new information.
- Report adverse events involving the co-administration of hepatitis C drugs with amiodarone to EPVC.

References:

FDA safety Communication (Click here)

Eosinophilia, Hypo-chromia, Leuco-cytosis and Erythro-cytosis induced by Clozapine

The Egyptian pharmaceutical Vigilance regional center in Sohag had received nine reports from the Minya QPPVs about different medical conditions for patients with varying ages and genders who had administered clozapine with another antipsychotic drugs for a long time then the automatic analysis had detected eosinophilia, hypo-chromia, leuco-cytosis and erythro-cytosis and the patients were suffering from chronic inflammation and sore throat which was recovered by Continuous administration of anti–inflammatory drug.

Clozapine: is an antipsychotic drug with a broad range of antipsychotic activity. The low affinity for D2 receptor deserves clozapine a unique profile, as its use is not associated with extrapyramidal side effects. However, due to a risk of agranulocytosis, the therapeutic indication has been restricted to schizophrenic patients resistant or intolerant to other antipsychotics.

Eosinophilia: defined as a blood eosinophil count of greater than 700/mm^3.

Hypo-chromia: mean that the corpuscular hemoglobin concentration is less than normal.

Leukocytosis: An abnormally large increase in the number of white blood cells in the blood, often occurring during an acute infection or inflammation.

Erythrocytosis: is a relative or absolute increase in the number of circulating RBC.

Recommendations:

1. It should be limited to patients with schizophrenic who are non-responsive or intolerant to antipsychotic medication with psychosis in Parkinson's disease when other treatment strategies have failed.
2. WBC and differential blood counts must be performed within 10 days prior to initiating clozapine treatment to ensure that the only patients with normal WBC counts and ANC (WBC ≥3500/mm3 and ANC≥2000mm3) will receive the drug. And then the WBC & ANC must be monitored weekly for the first 18 weeks and at least at four –week intervals thereafter .
3. If WBC < 3000 ($3*10^9$)& ANC <1500 ($1.5*10^9$):

   Immediate discontinuation Clozapine is mandatory at any time during Clozapine treatment, sample blood daily until hematological abnormality is resolved, Monitor for infection, Don't re-exposer the patient

4. It is generally recommended that clozapine should not be used in combination with other antipsychotics.

5. Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis.

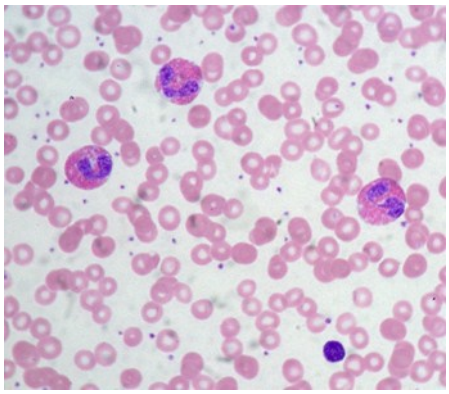
6. Treatment – resistant schizophrenic patients:

   A. The daily dose may be further increased in increments of 50 to 100 mg at half weekly or preferably, weekly intervals.

   B. Treatment should be maintained for at least 6 months.

   C. Anti-psychotic efficacy can be expected with 200 to 450 mg/day in divided doses. Larger portion at bed time

7. In psychotic disorders:
   A. The daily dose may be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level up to 300 mg/day within 2 to 3 weeks.
   B. The maximum dose of 100mg/day must never be exceeded.



References:

1. *FDA-Prescribing information of Clozaril tablets(Cozapine) (Click here)*
2. *EMEA-Evaluation of Leponex (Click here)*

Capecitabine / Multivitamin containing Folic acid – A case of major interaction, in Elbeheira governorate

The regional center in Alexandria received a yellow card from El Beheira governorate, concerning a fifty four years old male suffering from appendicular mucoid adenocarcinoma grade II.

Post operatively, the physician prescribed to the patient 6 cycles of combination chemotherapy (Xeloda + Irinotecan). Each cycle is for 21 days (14 days of treatment followed by 7 day rest period).

After the 4th cycle, the patient developed severe gastroenteritis and diarrhea. He was hospitalized with severe dehydration, metabolic acidosis with marked renal impairment.

He received IV fluids and antidiarrheal drugs, although the condition did not improve. At mid night the patient became on dialysis due to acute renal failure.

Hemodialysis was done for 3 consecutive days and then the case was stabilized.

Oncology consultants decided to stop the chemotherapy.

Later, it was discovered that the patient was using Centrum (multivitamin containing folic acid) during the chemotherapy (Xeloda + Irinotican).

Background:

Xeloda (capecitabine) is a fluoropyrimidine carbamate with antineoplasticactivity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is **converted to 5 -fluorouracil**.

It is used for colon, colorectal and gastric cancer. It may be used as a monotherapy or as a combination therapy.

The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min).The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 ml/min at baseline) is increased compared to the overall population.

Centrum is a multivitamin and mineral supplement. It is used to provide extra vitamins and minerals that are not taken in through the diet. Multivitamins and minerals are also used to treat vitamin or mineral deficiencies caused by illness, pregnancy, poor nutrition, digestive disorders, certain medications, and many other conditions. One of Centrum components is **"Folic acid".** <

Labeled information:

According to Xeloda Summary of product Characteristics (SmPC), it was stated under section (4.5 Interaction with other medicinal products and other forms of interaction) that:

Folinic acid has no major effect on the pharm cokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine. **The toxicity of capecitabine may be enhanced by folinic acid.** This may also be relevant with folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

Recommendations for Healthcare Professionals:

1. The Co-administration of Capecitabine with folate therapy may potentiate the pharmacologic effects of 5-fluorouracil (5-FU).
2. A lower dosage of 5-FU or the prodrug may be required.
3. Patients should be monitored closely for potential toxicities of 5-FU such as neutropenia, thrombocytopenia, stomatitis, gastrointestinal hemorrhage, severe diarrhea, vomiting, cutaneous reactions, and neuropathy.
4. Patients should be instructed to avoid taking folic acid supplementation or multivitamin preparations containing folic acid without first speaking with their physician.
5. Caution should be taken when receiving tablets containing multivitamins with chemotherapy.

References:

1. *Xeloda SPC (Click here)*
2. *Drugs.com: Interactions between Centrum and Xeloda (Click here)*
3. *Rxlist.com: Xeloda (Click here)*

Ceftriaxone and calcium containing diluents –Interaction

EPVC reminds Healthcare Professionals (HCP) of a well-known interaction that occur between (Ceftriaxone sodium) for Injection and calcium-containing IV solutions.

Ceftriaxone injection (cephalosporin Antibiotic) is used to treat certain infections caused by bacteria such as gonorrhea, Pelvic inflammatory disease, meningitis and infection of the lungs, ears, skin, urinary tract, bones, blood, joints and abdomen.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiv-

ing Ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line.

Although there were no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions, there's theoretical possibility for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates.

Therefore, the Prescribing Information advised that they should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites.

As a further theoretical consideration and based on the elimination pharmacokinetics of ceftriaxone, the Prescribing Information additionally stated that ceftriaxone and IV calcium-containing solutions ***should not be administered within 48 hours*** of each other in any patient.

On June 2007 the Prescribing Information was updated in "The Clinical Pharmacology, Contraindications, Warnings, Adverse Reactions And Dosage And Administration" sections to further clarify the subject.

Recommendations for HCP:

- Do not use diluents containing calcium, **such as Ringer's solution or Hartmann's solution**, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
- Precipitation of ceftriaxone-calcium can also occur when Ceftriaxone is mixed with calcium-containing solutions in the same IV administration line.

  Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site.
- However, in patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

References:

1. *DHPC by Roche dated May 2009 (Click here)*
2. *ROCEPHIN® label (Click here)*

NORCB Newsletter

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National Organization for Research & Control of Biologicals

Post Marketing Surveillance and Adverse Event Following immunization Department

Inside this issue:

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Global vaccination targets off-track

Progress towards global vaccination targets for 2015 is far off-track with 1 in 5 children still missing out on routine life-saving immunizations that could avert 1.5 million deaths each year from preventable diseases. In the lead-up to World Immunization Week 2015 (24–30 April), WHO is calling for renewed efforts to get progress back on course.

In 2013 nearly 22 million infants missed out on the required three doses of diphtheria-tetanus-pertussis-containing vaccines (DTP3), many of them living in the world's poorest countries. WHO is calling for an end to the unnecessary disability and death caused by failure to vaccinate.

In 2012, all 194 WHO Member States at the World Health Assembly endorsed the Global Vaccine Action Plan (GVAP), a commitment to ensure that no one misses out on vital immunization. However, a recent independent assessment report on GVAP progress rings an alarm bell, warning that vaccines are not being delivered equitably or reliably and that only 1 of the 6 key vaccination targets for 2015 is currently on track – the introduction of under-utilized vaccines.

Many countries worldwide have experienced large measles outbreaks in the past year, threatening efforts to achieve the GVAP target of eliminating measles in 3 WHO Regions by end -2015.

Actions to get back on track

A global collaborative drive for immunization, begun in the mid-1970s with the establishment of the Expaned Programme on Immunization in all countries achieved dramatic results, raising vaccination levels from as low as 5% to more than 80% in many countries by 2013. WHO estimates that today immunizations prevent between 2 and 3 million deaths annually and protect many more people from illness and disability.

The GVAP recommends three key steps for closing the immunization gap:

- integrating immunization with other health services, such as postnatal care for mothers and babies;
- strengthening health systems so that vaccines continue to be given even in times of crisis; and
- ensuring that everyone can access vaccines and afford to pay for them.

Although many countries are already vaccinating four out of five children with DTP3, a full one-third of countries are still struggling to reach the 'fifth child', meaning millions of children remain at risk of illness, disability or death because they are not getting the immunizations they need.

Critical operational needs to ensure wider vaccination and delivery on the ground, include:

- finding ways to simplify vaccination procedures in the field
- improving vaccination delivery to reach every last child, especially those living in remote and inaccessible areas
- ensuring vaccine affordability and strengthening vaccine supply chains

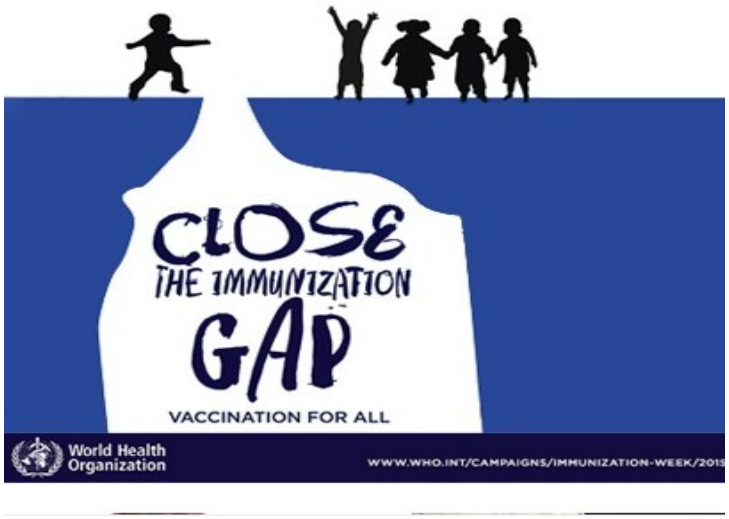
Training more health workers, skilled managers and providing supportive supervision

- Improving the quality of data collected by countries and using this to improve immunization operations
- Overcoming challenges posed by conflict, natural disasters and other crises;
- Increasing awareness and demand for immunization by communities
- Greater accountability linked to microplanning of vaccination operations and clear lines of responsibility.

https://youtu.be/jkfx4biGLYs **(Open video please)**

Reference

World Health Organization : (Click Here)



One dose of the powdered measles vaccine was not as effective as one dose of the traditional injected vaccine.

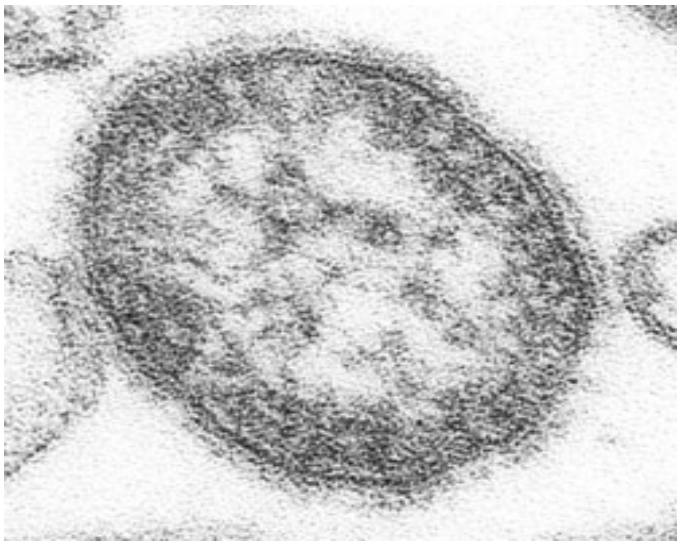
- In December, Indian manufacturer reported victory in a Phase I trial of its powdered measles vaccine. But now, it may have to go back to the drawing board, as results from a non-inferiority trial reported Thursday showed that one dose of the powdered candidate was not as effective as one dose of the traditional injected vaccine.

- The study, funded by the Bill & Melinda Gates Foundation and published in the *New England Journal of Medicine*, involved 2,004 children aged between 9 and 12 months. About half of them received the traditional jab, and the other half received the aerosolized inhaled vaccine. The inhaled vaccine did provoke an immune response, but one that was not as robust as that produced by the injected vaccine.

- Serum already manufactures an injected measles vaccine as well as one for measles and rubella. It announced in 2012 that it would donate 20 million doses of the latter to GAVI.

Reference

Fierce vaccines : (Click Here)



Healthcare systems could benefit from covering HPV vaccine in boys, study says

A new analysis shows that healthcare systems can prevent throat cancer cases and save in long-term treatment costs by covering the HPV vaccine in young boys. Currently, Australia, Canada and the United States recommend the jab for boys, but only cover it for young girls. Dr. Donna Graham of the Princess Margaret Cancer Centre in Toronto and her team found that Canada could save $6 million to $22 million for every 192,000 boys who are inoculated, and the savings could be greater in the U.S.

Reference
Fierce vaccines : (Click Here)

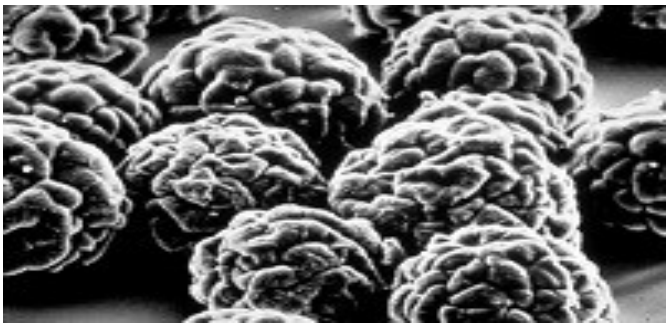
Gates Foundation, WHO fund synthetic polio vaccine development

Only a few hundred cases of polio are reported each year, but a synthetic vaccine could be the key to eradicating the virus for good. Scientists are teaming up to develop a synthetic vaccine in an effort to address some limitations of the existing oral vaccine.

The project, which will be funded by a $674,000 grant from the Bill & Melinda Gates Foundation and the WHO, was announced at the annual meeting of the American Association for the Advancement of Science.

According to BBC News, the current oral vaccine uses a weakened version of the virus, which provokes an immune response. However, the vaccine can cause infection in a few individuals, from whom the virus can spread to other, unvaccinated people. An artificial vaccine would not have this danger..

Reference
Fierce vaccines : (Click Here)



HIV vaccine trial kicks off in South Africa

Researchers have launched a clinical trial in South Africa--dubbed HVTN 100--to evaluate a candidate HIV vaccine regimen for safety and the immune response it triggers. The regimen is based on one tested in the U.S. Military HIV Research Program-led RV144 clinical trial in Thailand, which was the first study to demonstrate that a vaccine can guard against HIV infection. Results from the current trial--expected in two years--will help determine whether to take the vaccine regimen into a large-scale study.

Reference
Fierce vaccines : (Click Here)

What is Pharmacovigilance

According to the WHO, Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

What is the Egyptian Pharmaceutical Vigilance Center

With the increasing demand for patient's safety which is becoming more stringent, the regulatory authorities are facing an increased demand for patient welfare and safety. Thus, The Egyptian Pharmaceutical Vigilance Center (EPVC) is constructed within The Central Administration of Pharmaceutical Affairs (CAPA) Ministry of Health to be responsible for the collection and evaluation of information on pharmaceutical products marketed in Egypt with particular reference to adverse reactions. Furthermore, EPVC is taking all appropriate measures to:

1. Encourage physicians and other healthcare professionals to report the suspected adverse reactions to EPVC.
2. Necessitate the pharmaceutical companies to systematically collect information on risks related to their medical products and to transmit them to EPVC.
3. Provide information to end-users through adverse drug reaction news bulletins, drug alerts and seminars.

A call for reporting

Please remember that you can report suspected adverse reaction of medicines to EPVC, and adverse reaction following immunization to NORCB using the following communication information

Communications information

Central Administration of Pharmaceutical Affairs
Egyptian Pharmaceutical Vigilance Center
Pharmacovigilance Department

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt, PO Box: 11451
Phone: +202 – 23684288,
Fax: +202 – 23610497
Email: pv.center@eda.mohealth.gov.eg

www.epvc.gov.eg

National Organization for Research & Control of Biologicals
Post Marketing Surveillance and Adverse Event Following immunization Department

51 Wezaret El Zeraa Street, Agouza, Giza P.O. Box: 354 Dokki
Phone: +202 – 37 480 478 ext. 118
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Email: pmsdep@yahoo.com