Part I of II

EPVC Newsletter

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Egyptian Pharmaceutical Vigilance Center (EPVC)

Pharmacovigilance Department

Inside this issue:

Case Report from Sohag – Loss of concentration, drowsiness and fatigue induced by Imipramine

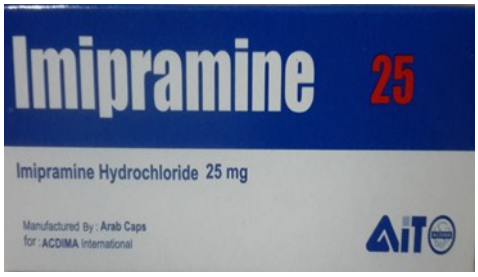
The Egyptian pharmaceutical Vigilance regional center at Sohag (**EPVC-Sohag**) has received a report about a female child patient who was treated from nocturnal enuresis by imipramine; a tablet once daily, then she suffered from loss of concentration, drowsiness and fatigue. After that her doctor reduced the dose to half tablet once daily then she recovered.

Imipramine hydrochloride USP, the original tricyclic antidepressant, is a member of the Dibenzazepine group of compounds, which affects chemicals in the brain that may become unbalanced, so it is used to treat symptoms of depression.

Imipramine is sometimes used to treat bed-wetting in children ages 6 and older.

Upon search it was found that:-

- Imipramine **pamoate is not approved for use in pediatric patients:** Pediatric Use Safety and effectiveness in the pediatric population have not been established, it is generally recommended that it should not be used in children because of the increased potential for acute over



dosage due to the high unit potency (75 mg, 100 mg, 125 mg, and 150 mg). Anyone considering the use of imipramine pamoate in a child or adolescent **must balance the potential risks with the clinical need.**

The safety and efficacy of imipramine as temporary adjunctive treatment for nocturnal enuresis in children *less than 5 years of age* have not been established**.**

- Imipramine used in treatment of Nocturnal enuresis (from the age of 5 years onwards and provided the possibility of organic causes has first been excluded).
- The initial daily dose is:

  5 to 8 years of age: 2 or 3 tablets of 10 mg,

  9 to 12 of age: 1 to 2 tablets of 25 mg,

  Older children: 1 to 3 tablets of 25 mg.

The higher doses apply to those cases which do not respond fully to treatment within one week.

The tablets should be given in a single dose after the evening meal, although children who wet their beds early in the night should be given part of the dose beforehand (at 4pm).

Once the desired response has been achieved the treatment should be continued (for 1 to 3 months), reducing the dose stepwise to the maintenance dose.

A daily dosage of 2.5 mg/kg should not be exceeded in children.

References:

1. *Tofranil label-FDA (Click here)*
2. *Tofranil label- TGA (Click here)*

Case Report from Sohag– Severe Neurotoxicity induced by Unitaxel

EPVC-Sohag has received a report about **Unitaxel 100 mg Vial** (Paclitaxel) about a female 35 years old patient who had administered Unitaxel 100 mg I.V. for treatment of breast cancer then she suffered from severe neurotoxicity after the first dose.

The patient had administrated Neurotonics and Gaptin to overcome this side effect but no response and the reaction continued.

Unitaxel (Paclitaxel): is a chemotherapy medicine. It works by slowing or stopping cancer cells from dividing and growing.

Indications:

1. Treating breast cancer, ovarian cancer and lung cancer.
2. Treating AIDS-related Kaposi's sarcoma.

Upon search it was found that :

* Although peripheral neuropathy is a common side effect, it usually causes only minor symptoms. If you develop severe symptoms, it is recommended to reduce the dose by 20% (25% for patients with Kaposi's sarcoma) in all subsequent courses of Unitaxel.
* Peripheral neuropathy is a dose-dependent, dose-limiting toxicity. Peripheral neuropathy occurs frequently with Unitaxel. The occurrence of grade 1 or 2 peripheral neuropathy does not generally require dose modification.
* When Unitaxel is used as monotherapy, if grade 3 peripheral neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of Unitaxel. For combination use of Unitaxel and carboplatin, if grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to grade 0 or 1 followed by a dose reduction for all subsequent courses of Unitaxel and carboplatin.
* Premedication: In order to minimise the possibility of hypersensitivity reactions due to

histamine release, patients must be premedicated before every treatment cycle of paclitaxel. Premedication should include corticosteroids (e.g. dexamethasone), antihistamines (e.g. diphenhydramine or promethazine) and an H2-receptor antagonist (e.g. cimetidine or ranitidine). The characteristic symptoms of hypersensitivity reactions are dyspnoea and hypotension (both requiring treatment), angioedema and widespread urticaria. In clinical trials, 2% of patients treated with paclitaxel experienced severe hypersensitivity. One of these reactions was fatal in a patient treated without premedication. Paclitaxel Injection Concentrate must not be used in patients who have exhibited hypersensitivity reactions to paclitaxel.

DOSAGE AND ADMINISTRATION:

i) **The neurotoxicity**, especially peripheral neuropathy, seems to be more frequent and severe with an infusion of 175 mg / m^2 over 3 hours (85% neurotoxicity, 15% severe) with an infusion of 135 mg / m^2 over 24 hours (25 % peripheral neuropathy, 3% severe) of paclitaxel in combination with Cisplatin.

ii) Repeat courses of Paclitaxel Injection Concentrate should not be administered to patients with solid tumors until the neutrophil count is at least 1.5 x 10^9 cells/L and the platelet count is at least 100 x 10^9 cells/L. Patients who experience severe neutropenia (< 0.5x 10^9 cells/L) or severe peripheral neuropathy should receive a dosage reduction by 20% for subsequent courses. The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

References:

1. *SPC of Abraxane-TGA: (Click here)*
2. *SPC of Paclitaxel-TGA (Click here)*
3. *SPC of Paclitaxel -France: (Click here)*

Case Reports from Sohag– lack of efficacy with Jilifen

EPVC-Sohag has received **two** reports about **JILIFEN 250Mcg/ml ampoule.**

Case one:

Adult male Neutropenic patient -50 years old- who had administered **Jilifen** (granulocyte growth factor) with no recovery as the patient WBC count was 0.3 and become 0.5 after ten days of treatment.

Case two:

Adult female Neutropenic patient - 43 years old- who was given **Jilifen** with delayed response to the drug which led to prolonged immunity suppression as the patient WBC count didn't increase.

***Jilifen (filgrastim)*:** is a hematopoietic agent. It works by stimulating the production of neutrophils (a type of white blood cells) by bone marrow.

Indications:

1. Decreasing the risk of infection in certain patients, including cancer patients who are receiving chemotherapy.
2. Raise the number of stem cells or to treat low white blood cell counts.

3. Increase survival in certain patients who are receiving radiation.
4. For other conditions as determined by your doctor.

Upon search it was found that :

- For each patient, the dose should be selected individually so that an ANC minimum value of 1.5×10^9 / l is achieved.
- A daily long-term use is indicated to provide adequate maintain neutrophil counts. The dose should be doubled if after 1-2 weeks of the ANC target value of 1.5×10^9/l has not been reached, and the dose should be halved if an ANC value of 10.0×10^9/ 1 is exceeded. A faster increase in the dose is indicated in patients with severe infections. Doses of more than 14.5 MU (145 micrograms) per kilogram of body weight per day are safe and have been well tolerated.
- Jilifen is a single – point (ready to be broken) ampoule, it is suggested that the point be sterilized with something like alcohol cotton swab before use.
- If via intravenous drip route, mix with 5% glucose solution or physiological saline before injection .do not mix with other medicines.
- When administered intravenously, the speed should be as slow as possible.
- Store Jilifen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Avoid freezing Jilifen. If frozen, thaw in the refrigerator before giving a dose. Throw away (dispose of) Jilifen if it has been frozen more than 1 time.
- Store Jilifen in the carton to protect from light until you are ready to use it.
- Do not leave Jilifen in direct sunlight.
- Avoid shaking Jilifen.
- Jilifen can be left out at room temperature for up to 24 hours. Throw away (dispose of) Jilifen that has been left at room temperature for longer than 24 hours.
- Jilifen acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore in patients with reduced precursors neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumor).
- The effects of Jilifen in patients with substantially reduced myeloid progenitors have not been studied.

References:

- *FDA:-Neupogen label (Click here)*
- *MHRA-DHCP communication (Click here)*
- *TGA: Neupogen label (Click here)*
- *Drugs.com– side effects (Click here)*

Case Report from Cairo– Death due to sudden cardiac arrest in patient received Epilog

The regional center in Cairo has received a yellow card concerning a 70 years old male who had administered Epilog ampoule 250mg (Phenytoin) (four ampoules IV infusion OVER 15-30 MIN as a loading dose) for Convulsions according to his physician's prescription.

This led him to death due to sudden cardiac arrest after 10 min from starting infusion.

Phenytoin sodium inhibits the spread of seizure activity in the motor cortex*. Phenytoin thereby reduces the over-*

activity of brain stem centers responsible for the tonic phase of grand mal seizures.

Convulsion: *An abnormal, involuntary contraction of the muscles most typically seen with certain seizure disorders. The term convulsion is sometimes used as a synonym for seizure, but not all seizures are characterized by convulsions***.**

Labeled information:

According to Phenytoin Summary of product Characteristics (SmPC) :

it was stated under section (4.2 Posology and method of administration) that: " For the control of status epilepticus, ***150 to 250 mg should be given by slow intravenous injection at a rate not exceeding 50 mg/ minute to avoid hypotension. This dose can be repeated if necessary after 30 minutes.*** *A previously untreated adult may require 10-15 mg/kg. The loading dose is then followed by a maintenance dose of 100 mg given orally or intravenously every 6-8 hours.* ***In geriatric patients with heart disease, it has been recommended that the drug be given at a rate of 50 mg over 2-3 minutes****."*

It was stated under section (4.4 Special warnings and precautions for use) that *"Rapid administration by the intravenous route may result in hypotension. The most notable signs of toxicity associated with the intravenous use of this drug are cardiovascular collapse and/or central nervous system depression. If the preparation is given too rapidly or in excess, severe cardiotoxic reactions and fatalities due to depression of atrial and ventricular conduction and ventricular fibrillation, respiratory arrest and tonic seizures have been reported, particularly in elderly or gravely ill patients. In these patients, the drug should be administered at a rate not exceeding 25 mg/minute, and if necessary, at a slow rate of 5 to 10 mg/minute."*

According to Phenytoin Sodium Injection Summary of product Characteristics (SmPC) It was stated under section (4.4 Special warnings and precautions for use) that

"Because adverse cardiovascular reactions have occurred during and after infusions, careful cardiac monitoring is needed during and after the administration of intravenous Phenytoin. Reduction in rate of administration or discontinuation of dosing may be needed.

Recommendations for Healthcare Professionals:

1. Phenytoin Injection should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter.
2. The dose is 150 to 250 mg should be given by slow intravenous injection at a rate not exceeding 50 mg/minute to avoid hypotension. This dose can be repeated if necessary after 30 minutes.
3. Elderly Patients: Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.
5. In geriatric patients with heart disease, it has been recommended that the drug be given at a rate of 50 mg over 2-3 minutes.
6. Intravenous phenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency.
7. Continuous monitoring of the electrocardiogram and blood pressure is essential.
8. Cardiac resuscitative equipment should be available.
9. The patient should be observed for signs of respiratory depression.
10. If administration of intravenous Phenytoin Injection does not terminate seizures, the use of other measures, including general anaesthesia, should be considered.
11. Other measures, including concomitant administration of an intravenous benzodiazepine such as diazepam, or an intravenous short-acting barbiturate, will usually be necessary for rapid control of seizures because of the required slow rate of administration of phentoin.
12. Determination of phenytoin serum levels is advised when using Phenytoin Injection in the management of status epilepticus and in the subsequent establishing of maintenance dosage. The clinically effective level is usually 10-20 mg/1 although some cases of tonic-clonic seizures may be controlled with lower serum

levels of phenytoin.

13. Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak plasma levels may require up to 24 hours.

References:

[1] Phenytoin Injection BP - Summary of Product Characteristics (SPC) - (eMC) (Click Here)

[2] Dilantin - Summary of Product Characteristics (SPC) - FDA (Click Here)

Case Report from Cairo– Intrapulmonary hemorrhage & intracranial hemorrhage associated with Survanta

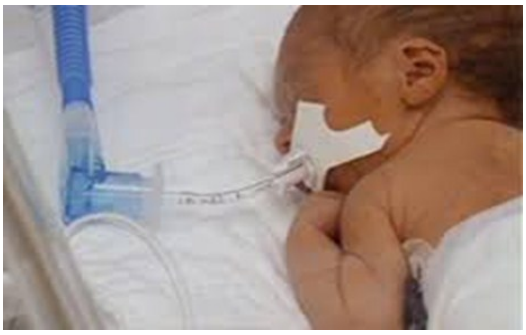
The regional center in Cairo has received a yellow card concerning a 1 day old neonate that received Survanta 100 mg intra-tracheally once as per her physician's prescription for treatment of **Respiratory Distress Syndrome (RDS)**. This led to intrapulmonary hemorrhage, convulsions and intracranial hemorrhage, and then the patient died at the age of 7 days.

Survanta (beractant): is indicated for treatment of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in new born premature infants with a birth weight of 700g or greater and who are intubated and are receiving mechanical ventilation.

Respiratory Distress Syndrome: develops in premature infants because of impaired surfactant synthesis and secretion leading to atelectasis, ventilation-perfusion (V/Q) inequality, and hypoventilation with resultant hypoxemia and hypercarbia. Blood gases show respiratory and metabolic acidosis that cause pulmonary vasoconstriction, resulting in impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes

The incidence and severity of respiratory distress syndrome are related inversely to the gestational age of the newborn infant.

Labeled information: "Summary of product Characteristics (SmPC)"



According to **Survanta** Summary of product Characteristics (SmPC) it was stated under section (4.8 Undesirable effects) that:

"*Intracranial haemorrhage has been observed in patients who received either beractant or placebo. The incidence of intracranial haemorrhage in all patients is similar to that reported in the literature in this patient population. Pulmonary haemorrhage has also been reported. Blockage of the endotracheal tube by mucous secretions has been reported.*

Recommendations for Healthcare Professionals:

- There are very important parameters to be taken into consideration before administering Survanta

  A. **Experience of the Supervising Clinician**
  B. **Oxygenation and Lung Compliance**
  C. **Cardiovascular Effects**
  D. **Respiratory Effects**

- Survanta is intended for intratracheal use only.
- Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.
- Marked improvements in oxygenation may occur within minutes of the administration of Survanta. Therefore, frequent and careful monitoring of systemic oxygenation is essential to avoid hyperoxia.
- Following Survanta administration, monitoring of the arterial blood gases, the fraction of inspired oxygen and ventilatory change is required to ensure appropriate adjustments.
- Survanta can rapidly affect oxygenation and lung compliance. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving Survanta should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.
- During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

References:

1. Drugs.com FDA prescribing information (Click here)

2. Medscape.com: Survanta, Lung Surfactants (Click here)

3. Medicines.org.uk/emc (SmPC) 03-Aug-2015 (Click here)

4. Rxlist.com Survanta, Drug description (Click here)

5. Pubmed: Effect of exogenous pulmonary surfactants on mortality rate in neonatal RDS (Click Here)

6. Medscape.com: Respiratory Distress Syndrome (Click here)

Inspection department warning regarding Betaferon Vial counterfeit

It was found that there are some counterfeited Betaferon Vials in the Egyptian market, where the original packages are illegally refilled with ingredients of unknown source and its Expiry date label is replaced.

The Pharmaceutical inspection department at CAPA recommends obtaining Betaferon vials from authorized distributors ONLY, and execution of all empty packages.

Necessary legal actions would be taken against unauthorized distributors selling Betaferon, and pharmacies who gets Betaferon from unauthorized stores or unknown sources.

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National Organization for Research & Control of Biologicals

Post Marketing Surveillance and Adverse Event Following immunization Department

Inside this issue:

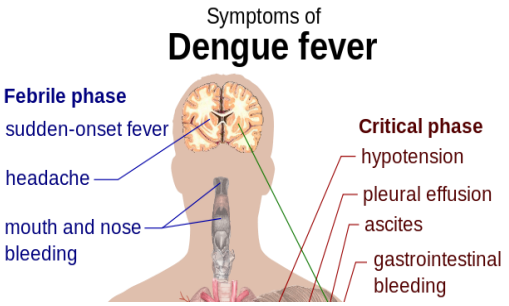
Egyptian district reports 253 dengue fever cases

The National International Health Regulations Focal Point of Egypt recently informed the World Health Organization that there has been a dengue fever outbreak in the Dayrout District of Assiute Governorate. The Dayrout Fever Hospital accepted 253 new dengue fever cases in October. Patients showed symptoms of acute febrile illness, such as headache, fever, abdominal pain, body aches, diarrhea and vomiting. Some of the patients were living in the same house, showing the spread of the illness. All of the patients have shown strong responses with medical care. They did not show any additional complications at the hospital and no deaths were reported. The physicians took multiple samples of blood and serum as well as oropharyngeal swabs.

The test results from ELISA and PCR, based at the Central Public Health Laboratories, showed that 28 of the 118 samples had dengue virus Type I.
A group of national experts -- including entomologists, laboratory personnel, epidemiologists, and sanitation personnel -- have visited the affected area and will perform investigations into the spread of the virus.

Reference

Vaccine News Daily: (Click Here)



WHO reports measles vaccinations are stalling globally

The World Health Organization (WHO) has reported that an estimated 17.1 million people have been saved from the measles virus since 1990 due to increased vaccination efforts, they announced on Thursday. Despite this, the Centers for Disease Control and Prevention (CDC) and the WHO have reported that progress toward total immunization has stalled during the past four years. Between 2000 and 2010, measles vaccine coverage increased to 85 percent. WHO's director of the Department of Immunization, Vaccines and Biologicals, said "If children miss routine vaccination and are not reached by national immunization campaigns, we will not close the immunization gap."The WHO reports that global milestone and measles elimination goals will likely not be achieved on time considering current trends. Primary challenges to meeting global targets for vaccination remain in the form of gaps in vaccination programs that lead to outbreaks of the disease. Gavi, the Vaccine Alliance, played a role in large-scale campaigns in high-risk countries that has improved the control of the disease, including the Congo and Pakistan.

Reference

Vaccine News Daily: (Click Here)

MERS outbreak spreads through facilities in Saudi Arabia

Health investigators have been tracing the origins of a MERS outbreak that spread throughout several health care facilities in Taif, Saudi Arabia. The Middle East respiratory syndrome coronavirus (MERS-CoV), is a respiratory pathogen that caused 38 cases from September 2014 to January 2015. These cases were found in four health care facilities throughout Taif. Twenty-one of the 38 patients died from their diseases. Records from public as well as clinical health data demonstrated that 13 of the MERS patients had served as health care personnel (HCP). Fifteen of the patients, four of whom were HCP patients, were linked to an infection at a dialysis unit. Three more of the HCP patients who had been in the dialysis unit showed evidence that they had contracted MERS-CoV infections. Researchers amplified viral RNA taken from acute-phase serum specimens showed the relations between the patients. Fifteen of the patients submitted their specimens. The scientists ran a series of full spike gene-coding sequencing from 10 of the patients to create a discrete clusters. Nine of the specimens from patients showed they were closely connected. Other gene sequences from the samples showed the cases were not connected by location or time. This means that the viral transmission has not been found. The viral circulation has continued to spread through several health care facilities as the outbreak continued. This emphasizes that infection control and surveillance practices are crucial to eliminating outbreaks and preventing them in the future.

Reference

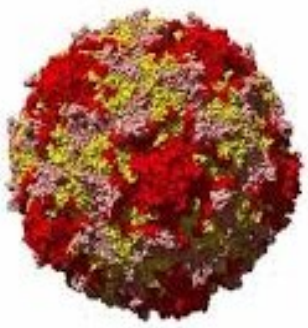
Vaccine News Daily: (Click Here)

New vaccine to protect Somali children from polio

Officials with the Somali government have introduced a novel vaccine that to protect children from polio and to maintain the nation's polio-free status. Fifteen months ago, health care workers in Somali confirmed the nation's last polio case. The new vaccine is being implemented to help the country maintain its goal of total elimination of polio.
In May 2013, there a polio outbreak in Somalia affected 199 people, mostly children. Last month, health officials declared that the outbreak had ended. The new vaccine is key to protecting children from polio and ensuring that we do not see a return of this incurable disease that has devastated so many young lives, UNICEF is committed to ensuring that Somali children receive the maximum protection and are given all life-saving vaccinations on time. Continued efforts and collaboration among all partners and communities will strengthen routine immunization and ensure this takes place.

Reference

Vaccine News Daily: (Click Here)



Study shows immune response from H1N1 flu vaccine is short-lived

Scientists from the Hong Kong Polytechnic University recently conducted a study that demonstrated that people who receive the H1N1 flu vaccine have a strong immune response for just two years. Health professionals first identified H1N1, or swine flu, in 2009 as the virus rapidly spread and killed countless people around the world. Now, it is one of the flues that spreads every season. Scientists previously thought that people with the H1N1 flu vaccine had strong immune responses against the virus for approximately 10 years. The researchers, divided into teams in Australia, China and the U.S., applied a mathematical model to show a map of how the various flu strains spread from 2006 to 2015. The results showed that H1N1 followed a "skip and resurgence" pattern in both Eastern Asia and Europe. For example, the virus was estimated to strike in 2011 and 2012, but there was no outbreak until the next flu season. The pattern is made clear with fundamental epidemiological theories. When a population has sustained immunity to the virus after the initial infection, the virus cannot outbreak like before, so it spreads elsewhere. When the immunity declines after two years, people become vulnerable to the virus again.

Reference:

Vaccine News Daily: (Click Here)

Study indicates protein mutation slows spread of coronavirus

Scientists recently found that a specific protein mutation within the coronavirus affects the spread of the virus in the body and neurovirulence of the virus itself. There has never before been this kind of discovery made concerning the coronavirus group, which causes approximately one-third of the cases of the common cold. Health professionals believe that the virus is also connected to the irritation or development of various neurological diseases including Alzheimer's, multiple sclerosis and encephalitis. The study involved analyses of over 60 human respiratory tract samples taken from patients who have human coronavirus infections. The scientists found a mutation based on the S protein, which changes the ability of the virus to settle in nerve cells. This, in turn, is connected to the virulence of the virus.

The Researchers noticed that the protein mutation did not affect the virus's ability to infect the central nervous system, but that the mutated virus was less pathogenic and neurovirulent, probably as a result of changes in the way it spread from neuron to neuron due to the action of cellular proteins known as proprotein convertases, which alter the structure of the viral protein, under these conditions, the coronavirus could more easily cause a persistent central nervous system infection. In virology, this phenomenon is known to trigger certain slow-developing neurological conditions or aggravate neurological diseases.

Reference

Vaccine News Daily: (Clik 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
Fax: +202 – 37480472
Email: pmsdep@yahoo.com