EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

The Egyptian Pharmaceutical Vigilance center

مركز اليقظة الصيدلية المصري

IN THIS ISSUE

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EPVC Mission

Pharmaceutical Vigilance administration is the way through which the processes for authorizing, regulating, monitoring and evaluating the safety of any pharmaceutical product or medical device take place, in addition to disseminating any safety information for public health programs, healthcare professionals, and the Egyptian citizen.

The Pharmaceutical vigilance administration is an integral part of the Central Administration of Pharmaceutical Care that works on the enhancement of the pharmaceutical services to guarantee safe and effective use of medications in Egypt, under the patronage of the Egyptian Drug Authority.

Newsletter

February 2023

Volume 14 **Issue 2**

Local Alert: Sub-standardized and Falsified (SF) Product

Egyptian Drug Authority Alert Regarding Voltaren 75mg/3ml 6 ampouls Counterfeit

The Egyptian Drug Authority (EDA) through the Central Administration of Operations announced an alert regarding presence of counterfeited Voltaren 75mg/3ml 6 ampouls in the market. EDA is quarantining the counterfeited batch number Y2607 .

EDA distributed and published circular with all data concerning the counterfeited product and how to differentiate between the original and counterfeit packs on EDA's website *(Click here)* .

The Egyptian Pharmaceutical Vigilance Center is encouraging public to report any detected packs through *(Click here)*.

Original

Counterfeit

Egyptian Drug Authority Alert Regarding Linezolid 600 7 film coated tablets Counterfeit

The Egyptian Drug Authority (EDA) through the Central Administration of Operations announced an alert regarding presence of counterfeited Linezolid 600 7 film coated tablets in the market. EDA is quarantining the counterfeited batches with Lot numbers H18116 - H .

EDA distributed and published circular with all data concerning the counterfeited product and how to differentiate between the original and counterfeit packs on EDA's website *(Click here)* .

The Egyptian Pharmaceutical Vigilance Center is encouraging public to report any detected packs through *(Click here)*.

Original

Counterfeit

Direct Healthcare Professional Communication (DHPC): Hydroxyethyl Starch Solution for Infusion– Reminder of Safety Measures to Minimize Risk of Kidney Injury and Death

EPVC in agreement with marketing authorization holders (MAH) of products containing Hydroxyethyl starch would like to inform you of the following:

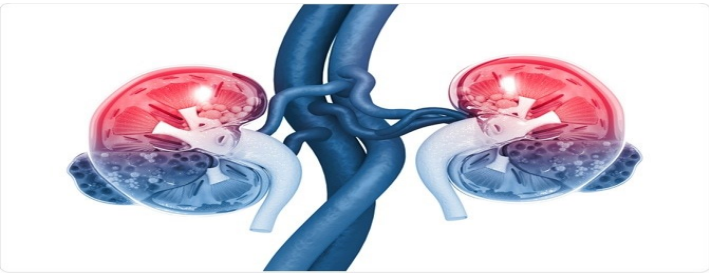
Summary:

- In 2013 the use of Hydroxyethyl Starch (HES) solutions for infusion was restricted because of an increased risk of kidney injury and mortality in certain patient populations.
- Despite extensive measures in place to protect vulnerable patient populations, final results of a drug utilization study have shown continued high non-adherence to the product information including non -adherence to contraindications.
- According to EDA technical committee decision; Hydroxyethyl starch infusion must not be used in patients with sepsis, kidney impairment, burns or critically ill patients.
- It can be used when in need in case of severe bleeding in emergency situations.
- Ensure the proper and safe use of its Hydroxyethyl starch (HES)-containing infusion solutions according to their approved product information (the treatment of hypovolaemia in adults and children only if crystalloids are not sufficient to stabilize the patient, and if the anticipated benefit justifies the risk)..

Background on safety concern:

Hydroxyethyl starch (HES) solutions for infusion are artificial colloids for volume replacement and are currently indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone were not considered sufficient. HES containing products have been the subject of several European assessments of their benefit risk balance over years.

In October 2013, a safety review was completed about an increased risk of kidney dysfunction and mortality in patients with sepsis or critical illness in large randomized clinical trials. The review concluded to restrict the use of HES solutions for infusion to the current indication. The product information was updated, including



new contraindications and warnings.

In October 2017, an additional review of the results of two drug utilization studies (DUSs) was performed. These studies raised concerns because key restrictions are not adhered to in clinical practice and that there was use in contraindicated populations.

Subsequently, in 2018, additional measures have been put in place to reinforce adherence to the authorized conditions of use, including restricting supply of HES solutions for infusion only to hospitals/centers where healthcare professionals expected to prescribe or administer them have undergone a mandatory training on the appropriate conditions of use (i.e. a controlled access programme), and more prominent warnings on the packaging of these solutions. Physicians were advised not to use HES solutions for infusion outside the terms of the marketing authorization as this could result in serious harm to their patients. The marketing authorization holders were requested to conduct an additional DUS to check adherence to the product information, and to demonstrate the effectiveness of these risk minimization measures.

In February 2022, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessed the final results of this DUS and concluded that non-adherence to the product information remains despite the extensive additional risk minimization measures implemented in 2018.

The purpose of this communication is to remind healthcare professionals not to use HES solutions for infusion outside the terms of the marketing authorization as detailed in the summary of product characteristics (SmPC) as this could result in serious harm to their patients.

References:

EMA (Click here)

Case Report from Cairo: Insulin - lack of Drug Effect

The regional center in Cairo received a case report regarding a 42-year-old male patient with Diabetes Mellitus. He has been taking 20 IU of insulin human/isophane (NPH) insulin human in the ratio 30/70 suspension once daily for Diabetes Mellitus.

He hadn't felt that the product was effective in the last 2 months. He tried a different batch from another governorate, but the same outcome still occurred.

His treating physician increased the dosage for him after his blood results turned abnormal. With no change, the dose was increased to 40 IU divided into 2 doses each day, and subsequently to 80 IU divided into 2 doses. At the final dose, the medication started to work.

The reaction was considered non serious.

No concomitant drugs were administered, the diet and lifestyle of the patient were not changed before dose increase .

Background:

Human Insulin: There are different types of insulin depending on how quickly they work, when they peak and how long they last. Insulin is available in different strengths; the most common is100 IU.

Inside the pancreas, the hormone insulin is made in the beta cells, which are part of the Islets of Langerhans. These islets also have alpha cells, which make glucagon, as well as delta cells. With each meal, beta cells release insulin to help the body use or store the blood glucose (blood sugar) it gets from food .

Types of Insulin

- **Rapid-acting insulin**, begins to work about 15 minutes after injection, peaks in about one or two hours after injection, and last between two to four hours. Types: insulin aspart, Insulin glulisine), and insulin lispro.
- **Intermediate-acting insulin** generally **reaches** the bloodstream about two to four hours after injection, peaks four to 12 hours later, and is effective for about 12 to 18 hours. *Types: NPH*
- **Long-acting insulin** reaches the bloodstream several hours after injection and tends to lower glucose levels up to 24 hours. *Types: degludec, detemir, and glargine*
- **Ultra-long-acting** reaches the blood stream in six hours, does not peak, and lasts about 36 hours or longer. *Types: glargine."* [1]

Case Report from Cairo: Insulin - lack of Drug Effect Continued

"Insulin human/isophane (NPH) insulin human mixture is a dual-acting human insulin. It is a biphasic formulation containing both fast-acting and longer-acting insulin. It is administered subcutaneously by injection in the thigh, the abdominal wall, the gluteal region or the deltoid region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Insulin suspensions are never to be administered intravenously. Injection into a lifted skin fold minimizes the risk of unintended intramuscular injection." [2]

Insulin Antibody Syndrome (EIAS): One of the underlying causes of Insulin lack of Effect is Exogenous Insulin Antibody Syndrome that leads to severe uncontrollable glycemic fluctuations. "EIAS is a rare immune disorder caused by insulin antibodies (IAs) that triggers severe uncontrollable glycemic fluctuations in some patients. The underlying mechanism is attributed to the reversible binding of insulin to IAs (insulin antibodies) [association/binding, followed by dissociation to free insulin]." [2]

"First isolated in 1956, insulin antibodies were shown to be present in 98% of patients who utilized insulin when only insulins derived from animal sources were available. Since that time, with the use of more purified insulins the incidence has dropped significantly but EIAS still occurs with the use of both human and analogue insulins. Some analogues have shown decreased antibody formation but there is no consistent recommendation for changes in insulin formulation to decrease insulin antibodies.

Exogenous insulin antibody syndrome (EIAS), which rarely occurs in the patient with type 1 diabetes, results in antibody-induced insulin resistance, hyperglycemia, ketosis, ketoacidosis, and hypoglycemia when insulin is released from the saturated insulin antibodies." [4]

Labeled information:

According to insulin SmPC section "Adverse Reactions ":

"Immunogenicity: As with all therapeutic peptides, insulin administration may cause anti-insulin antibodies to form." [5]

Case Report from Cairo: Insulin - lack of Drug Effect Continued

Recommendations for Healthcare Professionals :

1. Antibodies to exogenously delivered insulin are common with insulin treatment but are not often clinically significant.
2. IgG antibodies are the most common while IgE antibodies are the cause of insulin allergy.
3. At high titers, IgG antibodies may limit insulin action which could delay or diminish insulin action.
4. Rarely, antibodies can be agonists to the insulin receptor and cause hypoglycemia (usually postprandial hypoglycemia).
5. The development of antibodies depends on the purity, molecular structure, and storage conditions of the insulin administered as well as patient factors such as age, HLA type, and delivery route.
6. Most common when patients are exposed to cow or pork insulin, rather than only to human or analog insulins.
7. Insulin auto-antibodies, in people not previously treated with insulin, are at risk of developing type 1 diabetes.
8. React equally to analog insulin and unmodified human insulins.
9. Radioligand binding (RLB) assays are the most common assay used for measurement of insulin antibodies.
10. Gel filtration chromatography can identify insulin immunocomplexes with addition of exogeneous insulin to diagnose insulin autoimmune syndrome without necessarily using radiolabeled reagents.
11. Most studies show no relationship between the presence of insulin antibodies and complications such as nephropathy, retinopathy, and neuropathy.
12. Rarely, antibodies bind differently to different insulins from different species; clinical improvement may result from switching insulin sources [4].
13. No relationship between the level of insulin antibodies and the dosing of basal insulin or hemoglobin A1c has been noted.
14. No relationship between insulin dose and development of antibodies has been shown in clinical trials; therefore, antibodies are only a cause of insulin resistance when found in unusually high titer.
15. The presence of insulin antibodies does not prove that they are causing insulin resistance or hypoglycemia.
16. IgG insulin antibodies are rarely pathogenic, so attributing insulin resistance to antibodies is valid only when very high titer and only having ruled out more common causes." [6]

References:

1. *American Diabetes Assocciation* (Click here)
2. *EMA* (Click here)
3. *Journal of Clinal Apheresis* (Click here)
4. *Springer* (Click here)
5. *FDA* (Click here)
6. *Johns Hopkins Medicine* (Click here)

Egyptian Pharmaceutical Vigilance Center Training in East Medical District Healthcare Units

In the context of the vision and mission of the Egyptian Pharmaceutical Vigilance Center (EPVC) in spreading the awareness of the pharmacovigilance and the culture of reporting side effects among the Healthcare professionals to promote the safe and effective use of the different pharmaceutical products and to promote the pharmaceutical care, the center conducted training on pharmacovigilance organized by East medical district, attendees were 12 of the pharmacists from different healthcare units.

The training included a lecture and a workshop on the basics of Pharmacovigilance, its importance, and how to report adverse events and other safety information related to the different pharmaceutical products such as medicines, vaccines, biological products, and medical devices.

Egyptian Pharmaceutical Vigilance Center (EPVC) Decentralization Trainings for Raising Reporting Awareness

The decentralization Program is being continued with pleasure by the Egyptian Pharmaceutical Vigilance Center (EPVC). New cases were received through the national database, and additional organizations, such as Leprosy centers in the MoHP's preventative sector, were added to the programme.

Regarding the received cases, we are delighted to update them and provide comments to the coordinating organizations in an effort to improve the quality of the cases submitted through the national database.

Also, EPVC wishes to extend its appreciation to all coordinative organizations for their efforts and best wishes for the future.

Together for Safe Medicine Initiative Progress

We are pleased to announce that the third wave of the EDA initiative "together for safe medicine", had ended successfully on 15 January 2023. This comes following the success of the first and the second waves where initiative activities continued from December 2021 till January 2023.

The three waves included 315 shared pharmacists from 309 pharmacies who have benefited through practicing pharmacovigilance science in their community and hospital pharmacies with 34 top achiever pharmacists, from the whole 27 governorates all over Egypt. Egyptian Pharmacovigilance center is extremely thankful for all pharmacists who participated in EDA initiative from the first three waves as they performed 219 different activities related to spreading pharmacovigilance science between HCPs and citizens all over Egypt also helped in increasing reporting rate and numbers of ADR reports on the national database to 1481 reports.

As a continuation of the Initiative's success, the Egyptian Pharmacovigilance center plans to Launch the registration for the fourth wave in March 2023 to allow more community and hospital pharmacies to participate in the EDA initiative "together for safe medicine" all over Egypt governorates.

Here is the photos of TOP achievers in the three waves of EDA initiative "together for safe medicine".

EPVC Tips

On Pharmacovigilance

Visit EDA website to find all any medicine- related news, updates and alerts *Click here*

You will find all EPVC Newsletters and DHPCs here

You will also find all alerts regarding counterfeited and falsified products released by Central Administration of Operations *here*

One report counts

A call for reporting

What is Pharmacovigilance

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug- related problem.

What is the Egyptian Pharmaceutical Vigilance Center?

With the increasing demand for patient's safety which is becoming more stringent, . The Egyptian Pharmaceutical Vigilance Center was established to be responsible for the safety monitoring of the pharmaceutical products throughout its lifecycle and it is the regulatory authority regarding Pharmacovigilance and its applications .

EPVC monitors the safety of all types of pharmaceutical products, including human medicines, biological products, supplements, cosmetics, veterinary medicines, medical devices, Biocides and pesticides

Please remember that you can report safety information of medicines to EPVC using the following communication information:

Communication information

The Egyptian Drug Authority (EDA)
Pharmaceutical Care Administration
The Egyptian Pharmaceutical Vigilance Center (EPVC)

The Egyptian Pharmaceutical Vigilance center
مركز اليقظة الصيدلية المصري

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Reporting link: www.edaegypt.gov.eg
https://sites.google.com/view/epvc-reporting/healthcare-professional-public-adverse-drug-event-reporting/reporting-other-adverse-drug-event-cases

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