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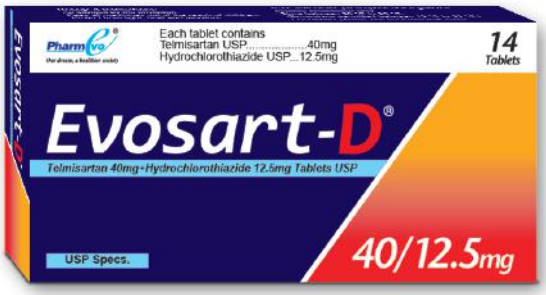
MEDICINE UPDATE

2017

Vol : 28 No : 03

Performs...

- Enhanced BP reductions with combination therapy.
- Better Metabolic Control



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3.1 Do biologic therapies (BTs) increase or lower risk for sepsis in rheumatoid arthritis (RA)?.

BTs increase risk for infection in patients with RA. Anti TNF and antileukotriene receptor antagonists may increase the risk of sepsis theoretically, compared to other medications for RA. However in animals, BTs given **before sepsis,**improved survival. What about the effects in humans?. German investigators examined outcomes of serious infections in 12,000 RA patients who have been treated with either BTs or conventional disease modifying anti rheumatic drugs (DMARDs). Follow up was for 10 years.

1017 serious infections mainly pneumonia, bone and joint infections were reported. 12% of these progressed to sepsis within 30 days. Patients with serious infections were older and had longer RA duration and more comorbidities than those without serious infections. Risk for subsequent6 sepsis and fatal outcomes, **were significantly lower** among patients taking BTs at the time of serious infections than among patients who were taking conventional DMARDs.

Comment: Although BTs heighten risk for infections, they nevertheless might mitigate the complications or severity that do occur in patients with RA. Currently, most Rheumatologists stop BTs when serious infection occurs. However, when the rheumatologic benefit of resuming BTs is thought to outweigh the excessive risk for infections, perhaps BTs need to be reinstated when active infection clears, given their favourable effect on the severity of subsequent infections, which might occur during their use.

Ref:Richter A. et al Ann.Rheum Dis. 2016 Sept; 75: 1667

3.2A new treatment that shrinks the plaques of Alzheimer Disease (AD).

Beta amyloid has been shown to be neurotoxic and is thought to play an important part in the pathogenesis of AD. In mice, therapies that inhibited production or cause regression of plaques – improved cognitive function. In humans, the results of the “amyloid hypothesis” has been disappointing.

A new monoclonal antibody – **Aducanumab (ACM) –** has been shown to enter the brain, bind selectively to Beta amyloid plaques and shrink them. This prompted an RC PC trial in 165 patients who had mild cognitive dysfunction or early AD, with PET scans positive for amyloid plaques. IV infusions given **monthly for one year** resulted in dramatic resolution of plaques in all patients on this drug. Cognitive decline was slower in the treated group compared to placebo.

Comment:ACM dramatically shrinks amyloid plaques, but cognitive improvement was not convincing because of underpowerment of the study. Further studies are awaited.

Ref: Sevigny J et al Nature 2016 Sept1; 537: 50.

3.3 Is sudden death due to neurological causes rare?.

Most cases of sudden death are assumed to be of cardiac origin and autopsies are rarely done. A San Fransisco team analysed the cause of death in 335 cases designated as sudden cardiac death by the medical examiner, after autopsies have been done. 5% of these were found to be sudden neurological deaths. The causes in descending order in these neurological deaths were found to be

1. Intracranial haemorrhage.
2. Secondary epilepsy.
3. Aneurismal subarachnoid haemorrhage.
4. Acute ischaemic stroke.
5. Aspiration pneumonia.

Patients on antithrombotic medication had an odds ratio of 3.9 for sudden neurological death. Sudden neurological deaths were the 2nd most common non cardiac cause of death after drug over dose.

Comment: Cases of neurological death can be misclassified, if a proper history is not available or if an autopsy is not done.

Ref:Kim A.S. et al Neurology 2016 Sept 16; e pub.

3.4 Can we predict adverse outcomes in patients with syncope?.

A prospective cohort of 4,030 adults presenting to 6 Canadian emergency departments (EDs) within 24 hours after syncopal events were analysed. Follow up period was 30 days. 9 clinical predictors were found for adverse events. They were:

1. Vasovagal syncope (- 2points).
2. Predisposition to vasovagal symptoms (- 1 point).
3. Abnormal QRS axis (+1 point).
4. QRS duration >130milli seconds (+1 point).
5. History of heart disease (+ 1point).
6. Systolic BP <80 mm or > 180mmHg (+2points)
7. Elevated troponin level (+2points).
8. Corrected QT interval >480milli seconds (+2points).
9. Cardiac syncope (+2points).

Note : "+ Means - More likely
- Means - Less likely"

A Score of -3 was associated with a serious adverse event in only 0.4% whereas a score of > + 6 was associated with an adverse risk of 41%.

Ref:Thirugnanasambandamoorthy V. et al CMAJ 2016 Sept 6; 188: E 289.

3.5Other than stroke – what are the adverse CV outcomes of atrial fibrillation (AF)?.

Patients with AF are treated with rate controlled drugs and anticoagulants to prevent stroke. Where possible, cryo ablation, radio frequency ablation and exclusion of the left atrial appendage have been undertaken to prevent embolic stroke. A meta analysis of 104 cohort studies was undertaken to determine other CV outcomes. N = 590,000 with AF. Follow up 3 -6 years. The following adverse events were noted - with higher risk for:

1. Peripheral artery disease.
2. All cause death.
3. Ischaemic heart disease.
4. Chronic kidney disease.
5. Sudden cardiac death.
6. CV related death.
7. Heart failure.

Comment: These associations do not establish causality. AF could be acting as a marker for an underlying predisposition to adverse CV and kidney outcomes.

Ref:Odutayo A. et al BMJ 2016 Sept 06; 354: i 44i2.

3.6 Does acupuncture alleviate chronic severe functional constipation (CSFC)?.

CSFC is diagnosed when all obstructive and metabolic factors are excluded and they have < 3 complete spontaneous bowel movements per week. 1075 such patients (age 17 – 85, 76% women) received electro acupuncture or sham electro acupuncture. They underwent 28 sessions over 8 weeks and were followed up for 12 additional weeks. **At 8 weeks**, weekly bowel movements increased 1.76 in the active group and 0.87 in the sham group. This was a significant difference. 38% had more than 3 bowel movements per week in the active group compared to 14% in the sham group. This difference was also significant.

Comment: Acupuncture at specific acupuncture points appear to stimulate the distal colon via parasympathetic activation. 25% of CSFC patients appear to benefit, although long term efficacy has not been established.

Ref:Liu Z. et al Ann.Intern.Med. 2016 Sept 13; (e pub).

3.7When should food be introduced in children to lower allergy risk?.

The American Academy of Paediatrics recommended in 2000 that high risk infants (those with eczema, other food allergies or atopic family history) should avoid dairy products until age 1, egg until age 2 and peanuts , nuts and fish until age 3. Recently researchers performed a meta analysisto shed further light on early food introduction and its association with allergic or autoimmune disease. In a study of 1915 participants, it was found that early egg introduction at 4-6 months and peanuts at 4 – 11 months was associated with lesser risk. It was concluded that children can **start all foods between ages of 4 – 12 months** with no excess risk for allergic or autoimmune disease.

Ref:Ierodiakonou D. et al JAMA 2016 Sept 20; 316 : 1181.

3.8Do GLP1 analogues increase the risk for breast cancer?.

Randomized trial data suggest that GLP1 analogues but not DPP4 inhibitors are associated with excess risk for breast cancer. A population based cohort study of 45,000 women (age >40) was undertaken, using the UK General Practice data base. Of these, 500 women used GLP1 analogues (Liraglutide, Exenatide) while 2,400 used DPP4 inhibitors (Sitagliptin, Saxagliptin). During mean follow up of 3.5 years, 549 women developed breast cancer. In adjusted analyses, GLP1 analogues were not associated with higher risk for breast cancer than were DPP4 inhibitors. In secondary analyses, 2-3 years of GLP1 analogue used was associated with higher risk for breast cancer
(Hazard ratio 2.7) but this excess risk disappeared after >3 years of use.

Comment: In this study, overall risk for breast cancer in women with Type 2DM treated with GLP1 analogues was similar to that with DPP4 inhibitors. The possible explanation for the excess risk associated in the first 3 years with GLP1 analogues but not with longer use – is that the loss of weight with GLP1 analogues made it easier to detect breast cancer. The other possibility was that the excess was due to cases of "cancer in situ", before GLP1 analogue was started, which later manifested as cancer. If at all, there is a slight increase in breast cancer incidence – this should be weighed against the benefit of improved glycaemic control, weight loss and reduction in adverse CV events.

Ref: Hicks.B.M. et al BMJ 2016 Oct 20; 355: i5340.
Bolen S.D. and Maruthur N.M. IBID: I 5519.

3.9 Congenital Zika virus syndrome.

Pregnant women with Zika virus infection may be asymptomatic or have only mild symptoms – primarily rash, headache and fever. When it occurs in the 1st trimester, the possibility of congenital abnormalities due to the virus is a distinct possibility. Microcephaly is the classical

presentation, although there are many other causes for this manifestation. Other abnormalities include,

a) Cerebral inflammation.
b) Focal calcifications.
c) Ocular abnormalities.
d) Arthrogryphosis.
e) Hydrocephalus with normal head circumference.

Ref:Melo A.S. et al JAMA Neurol 2016 Oct 3; e pub.
Roos R.P. IBID : e pub.

3.10Calciphylaxis – What is this?.

This is calcific uraemicarteriolopathy (CUA), because it is seen mostly in patients with end stage renal disease (ESRD).
It is characterized by painful necrotic lesions involving subcutaneous adipose tissue and the overlying skin. In a series of 101 patients seen at the MAYO clinic over 15 years – the following were noted.

a) 60% had end stage renal disease.
b) 20% did not have any renal impairment and 20% had only mild disease.
c) Median time to death was only 4 months.
d) One year survival was only 37%.
e) A high presence of thrombophilia with lupus anticoagulant and anti thrombin deficiency.

Treatment included the following:
a) Sodium thiosulphate locally.
b) Tissue plasminogen activator (TPA).
c) Hyperbaric oxygen.
d) Surgical debridement.
e) Parathyroidectomy.

Anticoagulation with warfarin

The best survival was seen in those who underwent d and e.

Ref:McCarthy J.T. et al Mayo ClinProc 2016 Oct; 91:1384.
El Azhary R.A. et al IBID : 1395.

3.11Snippets.

a)Paroxysmal Atrial fibrillation (PAF) –

PAF episodes which last **less than 20 seconds** are **not** associated with risk for stroke or other adverse clinical events. In these patients, risk of anticoagulants outweighs its benefits.

Ref:Swiryn S. et al Circulation 2016 Oct 18; 134: 1130

b) Short term caffeine in heart failure patients.
100mg of caffeine – the amount in a typical cup of coffee, taken hourly for 5 hours, was not associated with arrhythmias when compared to placebo. This was true even after exercise testing, when even the heart rate or peak oxygen consumption was no different from placebo.

Ref:Zuchinali P. et al JAMA Intern Med 2016 Oct 17; e pub.

c) Left main coronary artery stenosis- to stent or to bypass?.
This has been traditionally being treated by bypass surgery. In the randomized EXCEL trial, 2,905 patients with more than 70% LMCA stenosis, drug eluting stents were compared with bypass grafting. Follow up period was a median 3 years. At 3 years, stenting did not differ from bypass grafting in the main composite outcome. Early major adverse events (within 30 days) was 15% more commonly seen with bypass grafting. Late revascularization was more common (+5%) after stenting. Between 30 days and 3 years there was slight excess of adverse events with stenting.

Ref:Stone G.W. et al NEJ Med 2016 Oct 31; e pub.

Braunwald E IBID; e pub.

3.12 Is Proton Pump Inhibitor (PPI) use associated with excess risk for community acquired pneumonia (CAP)?.

Some observational studies have suggested that there is an association between PPI use and CAP. UK researchers studied the population database and conducted a cohort study, which compared risk for CAP in people exposed and people unexposed to PPIs. They found in a study of 160,000 adults that the adjusted risk (for various co morbidities) was 67% higher with PPI exposure in age and sex matched controls.

They also conducted a selfcontrolled case series where they compared the risk for CAP **within** individuals, during times of PPI exposure vs times of no PPI exposure. In this analyses of 48,000 adults who had CAP and some duration of PPI exposure – the risk for CAP was substantially higher during the 30 days **before** PPI prescription than during the 30 days after PPI prescription.

Comment: These results are reassuring to patients who use PPIs for valid reasons, but they don't justify casual, indefinite use of PPIs.

Ref:Othman F. et al BMJ 2016 Nov 15; 355: I 5813.

3.13 Can antipsychotics (APs) be withdrawn in Alzheimer's disease (AD)?.

APs are used in AD only when symptoms are severe or dangerous or cause substantial distress. Discontinuation of these drugs are normally attempted **within 4 months** of initiation, if adequate symptomatic response occurs, and patients have not experienced symptom recurrences after prior discontinuation attempts. Discontinuation is usually done by tapering off the dose gradually.

110 patients with AD whose psychosis or agitation responded positively to Risperidone 1 mg daily over 16 weeks were studied. After 16 weeks of treatment with improvement, they were randomized to continue Risperidone for further 32 weeks (group 1) or to 16 weeks of further Risperidone followed by 16 weeks of placebo (group 2) or placebo alone for the total of 32 weeks (group 3). After randomization, relapse occurred in 33% of patients continuing Risperidone and in 60% of those who discontinued them. The risk for relapse was highest in those who initially suffered **auditory hallucinations (91%)** while those with initial visual hallucinations did not show the same relapse risk. Patients with severe baseline **irritability / lability**also had a greatly increased risk of relapse with discontinuation (HR = 7.8).

Comment: Because severe baseline auditory hallucinations and irritability are prone to relapse, antipsychotic medication tapering or withdrawal should be undertaken very judiciously, if at all.

Ref:Patel A.N. et al Am.J.Psychiatry 2016 Nov 18; e pub.

3.14 In patients with atrial fibrillation (AF) and who require stenting for new ischaemic heart disease – which is the best anticoagulation strategy – Warfarin or Rivaroxaban?.

Anticoagulation treated patients with AF often received stents for coronary disease, prompting the need for additional dual antiplatelet therapy (DAPT). A multinational, manufacturer funded trial (PIONEER – AF) was undertaken where 2,124 patients with non valvular AF were randomized to 1 of 3 strategies after stent placement.

1. Low dose Rivaroxaban 15mg/d + 1 platelet inhibitor (eitherClopidogrel, Prasugrel or Ticagrelor) for 12 months.

2. Very low dose Rivaroxaban 2.5mg b.i.d + low dose Aspirin + a P2 Y 12 inhibitor (DAPT) for 1,6 or 12 months.

3. Adjusted dose Warfarin + low dose Aspirin + a P2 Y 12 inhibitor (DAPT) for 1,6,or 12 months.

Clinically significant bleeding was less common in group 1 (16.8%) vs Group 2 (18.0%) vs Group 3 (26.7%). The incidence of the composite efficacy end point of CV death + MI + stroke at one year were similar in the 3 groups.

Comment: Rivaroxaban at a low or very low dose + antiplatelet therapy was as effective as – and safer than – Warfarin + DAPT after stenting. It is unfortunate that this trial did not use the standard dose of Rivaroxaban 20mg, which is the dose that has been proven to be equivalent to Warfarin.

Ref:Gibson C.M. et al NEJ Med 2016 Nov 14; e pub.

3.15Does Cranberry juice prevent urinary tract infections (UTIs)?.

Cranberry juice retains a considerable reputation for both prevention and treatment for UTIs in women, despite the fact that studies frequently have failed to support its use. One common explanation for the negative data is the low concentrations of **proanthocyanidins** contained in both juice and cocktail. These molecules are known to inhibit E.coli adhesion in vitro and are thought to be responsible for the postulated antiseptic effects. Might concentrated cranberry capsules perform better?.

185 female nursing home residents were randomized to 2 cranberry capsules daily or placebo for 1 year. The total amount of proanthocyanidines contained in 2 cranberry capsules was equivalent to that in 20 oz of cranberry juice. Most of these women had urinary incontinence and 25% had a previous diagnosis of UTI. Monthly prevalence of bacteriuria and pyuria were similar in both groups, as were E.coli carriage rates.

Comment: This study joins others which do not support cranberry products as effective urinary antiseptics.

Ref:Juthani – Mehta M. et al JAMA 2016 Oct 27; e pub.
Nicolle L.E. IBID .e pub.

3.16 Are 5 Alpha Reductase Inhibitors (5 - ARIs) associated with erectile dysfunction (ED)?.

5 – ARIs are used to treat benign prostatic hyperplasia (BPH) and male pattern baldness (Alopecia). Because these drugs prevent the conversion of testosterone to dihydro Testosterone (DHT), it is thought that they might cause sexual side effects such as ED.

72,000 men (age about 40) with BPHand 12,000 men (age 18 – 59) with alopecia, who were free of sexual dysfunction were studied. In the BPH cohort, the drugs were ARIs Finasteride or Dutasteride only, Alpha blockers (Tamsulosin) only or both drugs. In the Alopecia cohort, men received either Finasteride or no treatment.

In the BPH cohort, use of 5ARIs with or without an Alpha blocker was not associated with ED compared with the use of an Alpha blocker only. It was noted that the risk for ED increased with **longer duration of BPH**, independent of 5 - ARI exposure. In the Alopecia cohort, use of Finasteride was not associated with excess risk for ED, compared with non use.

Comment: 5 - ARIs are not associated with excess risk for ED in men with BPH or Alopecia. Since risk for ED increases with longer duration of BPH, it is all the more important that ARIs should be prescribed for BPH early.

Ref:Hagberg K.W. et al BMJ 2016 Sept 22; 354: i 4823.

3.17What should be the duration of dual antiplatelet therapy (DAT) after drug eluting stent (DES) implantation – 6 months or 12 months?.

Guidelines recommend DAT for a minimum of **6 months** following DES implantation. Whether longer duration DAT is beneficial, especially in patients with diabetes, who have high ischaemic risk, is unclear. A meta analysis of 6 randomized trials was undertaken to determine the outcomes between short term (3 – 6 months) and long term (>12 months) of DAT therapy after DES in 112,500 patients (1/3rd had diabetes). One year out comes were as follows.

1. Incidence of major adverse CV events were higher in patients with diabetes than with non diabetics (HR 2.3).

2. Incidence of major adverse CV events was **not lower** with long term than with short term DAT in both diabetics and non diabetics.

3. In patients **without diabetes**, rates of major bleeding were **significantly higher** with long term DAT vs short term DAT.

Comment: Long term DAT did not lower the risk for major adverse CV events regardless of the presence or absence of diabetes. However it was associated with excessive risk for bleeding. Therefore diabetes per se should not be a driver for prolonging DAT over the mandatory period of 6 months after DES implant.

Ref:Gargiulo G. et al BMJ 2016 Nov 3; 355: i 5483.

3.18 A new treatment for aortic valve stenosis (AVS) – PCSK9 inhibitors?.

Elevated LPa and LDLC levels are considered causal risk factors for coronary heart disease and AVS. LPa consists of an LDL particle with apolipoprotein B 100 bound to apolipoprotein a – a large glycoprotein that resembles plasminogen. It has also been suggested to have a role in wound healing and to have prothrombotic and proatherogenic effects at elevated levels. PCSK9 is a serine protease that promotes the degradation of the LDL receptor. This will prevent elimination of LDLC resulting in elevated levels of LDLC and LPa. PCSK9 inhibitors prevent the destruction of LDL receptors thereby reducing both LDL and LPa. This has a potential of favourably preventing the occurrence and progression of aortic valve stenosis. Large statin trials although effective in LDLC lowering have failed to have an impact on aortic valve stenosis. Factors promoting aortic valve stenosis are bicuspid aortic valves, rheumatic fever, smoking, high BP, high cholesterol, diabetes and male sex. Further randomized studies are now awaited.

Ref:Langsted A. et al JCEM 2016 Sept.; 101: 3281 – 3287.

3.19 What is the relationship between non alcoholicsteatohepatitis (NASH) and obesity or diabetes Type 2 ?.

Non alcoholic fatty liver disease (NAFLD) may range from isolated steatosis to NASH, cirrhosis and eventually hepatocallular carcinoma. The prevelance of NAFLD among obese individuals may be as high as 65%. This value may be even higher in patients with Type 2 DM and obesity. NAFLD is frequently associated with insulin resistance which may be seen in both prediabetes and undiagnosed Type 2DM. Because of the insulin resistance, they may require more insulin to control hyperglycaemia. There is also a close relationship between dyslipidaemia and the presence of adipose tissue and hepatic insulin resistance, as seen in patients with both NAFLD and Type 2DM. Both these conditions are characterised by over secretion of VLDL driven by the high flux of fatty acids to the liver from dysfunctional adipose tissue.This leads to lower HDLC and to smaller, dense LDLC particles.

In a study of 154 obese patients divided into 4 groups :

Group 1 - no Type 2DM or NAFLD.
Group 2 – Type 2 DM without the NAFLD.
Group 3 – Type 2 DM with isolated steatosis.
Group 4 - Type 2DM with NASH.

The following were found:

a) In subjects who were obese alone the insulin resistance was increased by 30%.

b) Patients with diabetes and NASH had the highest insulin resistance.

c) Patients with diabetes and NASH had the most severe hypertriglyceridaemia but not hypertension.

d) Severity of NASH on liver histology closely relates with plasma triglyceride levels.

Comment: Patients with diabetes + NASH should be advised to undertake more aggressive life style interventions and medication to minimize high cardiovascular risk.

Ref:Lomonaco R. et al Diabetes Care 2016 April; 39: 632 – 638.

3.20What are the consequences to the offspring when the mother has diabetes during pregnancy?.

In a study of 632 youths (age 10 – 17 yrs) whose mothers presented with diabetes during pregnancy, the following results were seen (whether the mothers were diagnosed with diabetes prior to pregnancy or had gestational diabetes).

a) There was an increased risk for Type 2 diabetes in the offspring(3 fold higher risk).
b) They developed diabetes at an earlier age than those who have not been exposed.
c) The HbA1C was 0.3% higher.
d) There was reduced Beta cell function with a lower C peptide index, which may differ according to the racial and ethnic background.
e) Obesity in the offspring contributes to the emergence of Type 2DM.
f) Maternal effects are stronger than paternal.
g) The degree of gestational diabetes relates to the intensity of diabetes in the offspring.
h) There was a decreased ability to maintain glycaemic control compared to offspring who had no diabetic mothers.

Ref:Chernausek S.D. et al Diabetes Care 2016 Jan; 39(1): 110 – 117.

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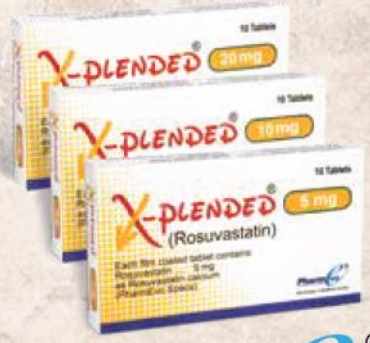
LDL-C	≥ 50% Reduction achieved	30% to < 50% Reduction achieved
Clinical ASCVD*	Age ≤ 75	Age > 75 or If not candidate for HIS**
Diabetes type I or II Age 40-75 years	Yes (10 year ASCVD risk ≥ 7.5%***)	Yes

* Atherosclerotic cardiovascular disease.
** High Intensity Statin.
*** ASCVD 10 year risk calculator.

This approach supports the use of statins to prevent both nonfatal and fatal ASCVD events.[1]

1. *Adapted from: Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline*



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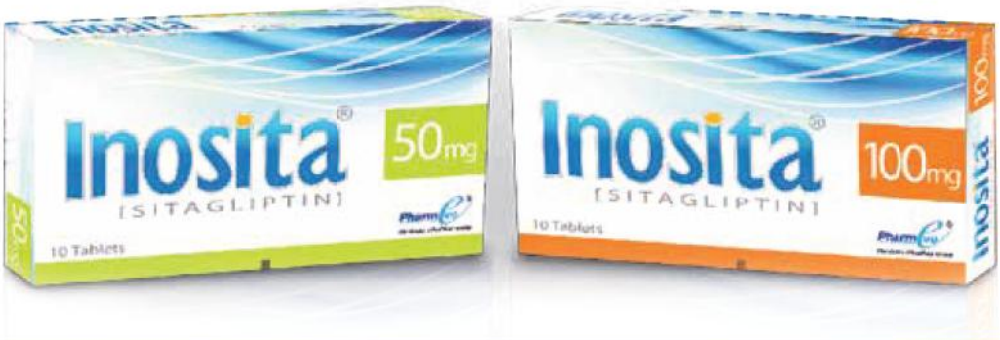

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