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MediScan New in Critical Care

Novel anticoagulants: bleeding risk and management strategies

Abraham NS, Castillo DL. *Curr Opin Gastroenterol* 2013; **29:** 676-683.

The novel oral anticoagulants (NOACs) include the direct thrombin inhibitor, dabigatran etexilate, and the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban. They were developed to overcome the limitations of warfarin by selectively blocking the key steps in the coagulation cascade leading to the fibrin clot. They have a rapid and predictable pharmacodynamic response with a once daily oral dose and do not require routine monitoring. However, there is a clinically significant risk of gastrointestinal (GIT) bleeding associated with the NOACs, which differs among the agents and with the indication for use. Data in this regard and with which to guide their use in different patient populations is limited.

In the atrial fibrillation population, the lowest risk of bleeding is associated with apixaban, with which it is nonsignificant. However the risk is increased by approximately 50% with both rivaroxaban and high-dose dabigatran (150 mg bid), especially in the elderly. With normal kidney function, the risk is not increased with a standard dose of dabigatran (110 mg).

In the post acute coronary syndrome population, where NOACs are prescribed in combination with dual antiplatelet therapy following percutaneous coronary intervention (PCI) or revascularization surgery in patients with atrial fibrillation, there is a three-fold increased risk of major bleeding. The risk-benefit threshold suggests that GIT bleeding risk may offset the ischaemic benefit. In this setting rivaroxaban had the lowest risk of bleeds and apixaban the highest.

The HAS-BLED score (considering hypertension, liver and renal function, stroke history, bleeding predisposition, labile INRs, age and drug use) is useful to help identify patients who might be at increased risk of GIT bleeds. However, it does not take into consideration *Helicobacter pylori* infection, corticosteroid use and gastrointestinal pathology, which may contribute to the risk of bleeding. Management strategies in the event of a serious bleed, include fluid resuscitation, withholding anticoagulant use and timely endoscopic treatment.

Novel oral anticoagulants and gastrointestinal bleeding: a case for cardiogastroenterology

Abraham NS. Clin *Gastroenterol Hepatol* 2013; **11:** 324-328.

Acute coronary syndrome (ACS) is associated with considerable morbidity and mortality. Dual antiplatelet therapy with aspirin and a thienopyridine, such as clopidogrel is usually precribed. Recently the American College of Cardiology Foundation and American Heart Association updated treatment guidelines to include the use of the newly approved thienopyridines, prasugrel and ticagrelor. Because they have been found to be superior to clopidogrel in comparative trials, these agents are now considered standard of care.

After ACS, patients are at the greatest risk of recurrent ischaemic events in the first 30 days and for up to a year. Even with dual therapy with aspirin and pasugrel or ticagrelor, the 1-year rate for stroke, cardiovascular death or myocardial infarction exceeds 11%. In patients with concomitant atrial fibrillation/flutter or after pulmonary embolism, anticoagulation is recommended in addition to dual antiplatelet therapy. Consequently, there is a considerable risk of GIT bleeding, which may offset the protective benefit of therapy. This is particluarly relevant in older patients and those with comorbidities. There is limited data to guide the use of NOACs in combination with antiplatelet agents and the risk of GIT bleeding with NOACs in post-ACS patients is still poorly understood. Trial data indicates that the number needed to harm (NNH) for a clinically significant bleed ranges from 20 to 200, depending on choice of drug, patient age and dose.

In this editorial, Dr Abraham describes the case of a 66 year old patient with acute coronary syndrome and PCI who experienced persistent occult and occasional overt GIT bleeding, which continued despite repeated enteroscopy. After he redeveloped unstable angina and new onset atrial fibrillation his cardiologist wanted to know if it was safe to reinstitute antiplatelet therapy. The risk of NOAC in this patient probably offsets any potential anti-ischemic benefit. Consequently, what to advise in this scenario is uncertain.

Reviewer: Dr Eric Hodgson obtained his MBChB from UCT. He then specialised in anaesthesia in Durban. He obtained his FCA in 1995 and subspecialty registration in critical care in 1998. He has a special interest in airway management, acute and chronic pain, Intensive Care and ethics. Following six years in private practice with Beck, Danchin and Partners in Durban, Dr Hodgson returned to government service as a Principal Specialist anaesthesiologist and intensivist at Addington Hospital. Since April 2012 Dr Hodgson has been the Chief Specialist anaesthesiologist at Inkosi Albert Luthuli Central Hospital and has continued as an honorary lecturer in the Department of Anaesthesia at the Nelson R Mandela School of Medicine in Durban.

Reviewer's comment

The NOACs such as the direct thrombin inhibitor dabigatran (Pradaxa®) or the factor Xa inhibitors rivaroxaban (Xarelto®), apixaban and edoxaban have been developed as replacements for warfarin and heparin in the prevention of venous thromboembolism (VTE) particularly after orthopaedic surgery. Indications that are being developed include treatment of VTE and prevention of stroke due to non-valvular atrial fibrillation. The real world experience of these drugs is represented in the articles reviewed above, which indicate there are risks to the use of NOACs particularly with concomitant use of antiplatelet agents. The benefit of the NOACs in terms of oral dosage and no requirement for monitoring may be offset by risks of bleeding and lack of reversibility should bleeding occur. Time will tell whether the risk-benefit ratio of the NOACs turns out to be favourable.

Antiplatelet therapy and proton pump inhibition: cause for concern?

Depta JP, Bhatt DL. *Curr Opin Cardiol* 2012; **27:** 642-650.

Despite use of dual antiplatelet therapy in acute coronary syndrome and/or after percutaneous coronary intervention, ischaemic events still do occur. Regardless of antiplatelet therapy, the predominant pathophysiological mechanisms responsible for these events include platelet activation and aggregation associated with high on-treatment platelet reactivity. Drug-drug interactions between proton pump inhibitors (PPIs) and clopidogrel have also been implicated in failure of antiplatelet therapy. PPIs are commonly prescribed to reduce the risk of gastrointestinal bleeds, which is exacerbated by antiplatelet therapy and is associated with significant morbidity and mortality in patients requiring dual antiplatelet therapy.

Clopidogrel is a prodrug that must be converted to its active metabolite by of the cytochrome P-450 (CYP) system. Because the majority of clopidogrel is inactivated by hepatic carboxylesterases after intestinal absorption, only approximately 10-15% of the initial prodrug dose is available for this conversion. PPIs are also metabolised by CYP 450 and may interefere with conversion of clopidogrel to its active metabolite by inhibiting various CYP enzymes, and in particular CYP 2C19. Both omeprazole and esomeprazole have been shown *in vivo* to significantly reduce the generation of clopidogrel's active metabolite. The effect of pantoprazole, lansoprazole and dexlansoprazole is less significant. There is no evidence of pharmacokinetic or pharmacodynamic interations between PPIs and ticagrelor.

Nonrandomised, observational studies of the clinical significance of PPI-clopidogrel drug interactions have produced mixed results. COGENT is the only randomised clinical trial that has studied the clinical significance of the drug interaction between omeprazole and clopidogrel and, when the study was discontinued at 180 days, there was no increase in the rate of cardiovascular events with combination therapy.

Current recommendations are that PPIs should be used in patients at high risk of bleeding. The selection of which PPI to use should be guided by patient preference, cost and availability.

Reviewer's comment

The theoretical risk of inhibition of cytochrome 2C19 by PPI agents such as omeprazole reducing the metabolism of clopidogrel, an antiplatelet agent used for secondary prevention of coronary thrombosis, to its active metabolite has long been recognised in the laboratory. Gastrointestinal bleeding in patients after treatment of coronary thrombosis is an important cause of morbidity and mortality. Withholding PPIs, where indicated, from these patients due to a theoretical risk of reduced clopidogrel activity cannot be justified.

Peptic ulcer disease: one in five is related to neither *Helicobacter pylori* nor aspirin/NSAID intake

Charpignon C, Legourgues B, Pariente A, *et al. Aliment Pharmacol Ther* 2013; **38:** 946-954.

Although *Helicobacter pylori* and use of nonsteroidal anti-inflammatory drugs or aspirin (NSAIDs) are the major causes of peptic ulcer disease (PUD), a proportion of ulcers are idiopathic. However, the actual prevalence of these ulcers and, indeed, if they actually exist (or are rather due to undiagnosed *H. pylori* or surreptitious use of NSAIDs or aspirin) is a subject of debate. The aim of this prospective observational study was to determine the prevalence and clinical characteristics of idiopathic PUD. The investigators evaluated medical records of 713 adult patients diagnosed with endoscopically proven PUD of the stomach and/or duodenum and/or erosive duodenitis over a period of 1 year in 32 public hospitals in different areas of France. Overall, the mean age was 62 years and 58% were male. Gastric ulcer was present in 42%, duodenal ulcer in 55% and both in 3%. The most common reasons for endoscopy were epigastric pain and bleeding. An aetiologic agent was identified in approximately 80%; namely *H.pylori* positive only (40%), NSAID/aspirin exposure only (19%); *H. pylori* positive and NSAID/aspirin exposure (20%). The remaining 22% of patients had neither *H. pylori* nor NSAID/aspirin exposure. Factors associated with *H. pylori*-associated PUD included more often younger age, male, past ulcer history, pain, duodenal ulcer and low death rate. Factors associated with NSAID/aspirin exposure included more commonly born in metropolitan France, female, bleeding at presentation, gastric ulcer and higher death rate. The mixed group had mixed characteristics of these two former groups. Idiopathic ulcers were associated with metropolitan origin, age (older than *H. pylori* PUD, younger than NSAID/aspirin PUD) and presence of comorbidities. The aetiology of these ulcers is unclear.

Reviewer's comment

Providing *Helicobacter pylori* eradication and/or withholding NSAIDs that may be providing significant cardiac protection (aspirin) or improved quality of life (e.g. in osteoarthritis) may not be necessary in up to 20% of patients diagnosed with peptic ulcer disease on endoscopy. The presence of *H. pylori* should be confirmed prior to initiation of eradication and indicated NSAIDs may be re-introduced, possibly under PPI cover.

To treat or not to treat: withholding treatment in the ICU

Godfrey G, Hilton A, Bellomo R. *Curr Opin Crit Care* 2013; **19:** 624-629.

Past studies have indicated that many terminally ill patients may remain on mechanical ventilation or in significant pain until their death, without their attending physician being aware of their preferences not to receive life-sustaining therapies. Decisions to limit life-sustaining therapy (DLLST) address this by empowering physicians to respect the patient's autonomy, protect them from non-beneficial treatment and fairly distribute ICU resources. This

can involve withholding ICU treatments under a variety of clinical and nonclinical situations, either before or after ICU admission. In conjunction with decisions to withdraw ICU treatments, DLLST may then be important with respect to an end-of-life decision (EOLD). In ICU as part of EOLD, DLLST are applied when the patient is not expected to survive, even with life-sustaining treatments.

Factors associated with expected poor outcomes and DLLST include older age, severity of the acute condition (e.g. burns, brain injury) and functional status, and lack of ICU resources. However, predicting the outcome is frequently difficult and differences of opinion amongst patients, relatives and healthcare professionals further complicates decision-making, especially when the patient is unable to communicate their own wishes. Although advanced directives may help to guide therapy, they must be reviewed regularly as the views of the individual changes. High quality, intensive communication and informed shared decision-making with the family are recommended, especially when the patient cannot speak for themself. However, many healthcare providers feel inadequately trained in end-of-life communication skills.

An improved understanding of reasons for, uncertainties and practices of DLLST is required among both the public and healthcare professionals.

Reviewer's comment

The majority of deaths in ICU now take place after withdrawal of therapy. This topic has been extensively discussed at the World Congress of Critical Care in Durban in September 2013 and will result in a number of publications. The important principle that should be applied by those caring for patients in the ICU is that they are advocates for their patients and should not be swayed by inappropriate demands from families, but make choices in the best interest of their patients. Continuing non-beneficial treatment that is delaying death, rather than saving life costs the patient in terms of suffering and society in terms of the squandering of scarce resources.

ETHICS CEU ARTICLE - BY ESMÉ PRINS-VAN DEN BERG, HEALTHCARE NAVIGATOR

MORE REGULATION … BE PREPARED!

Earlier last year changes were made to the Ethical Rules by the Health Professions Council of SA (HPCSA). On the one hand the professional conduct of practitioners that would be regarded as impermissible was broadened, whilst on the other a restriction in one of the Rules was removed. Shortly thereafter an amendment to the Competition Act became law, which would allow inquiries into market conduct. The first market to be investigated appears to be the health care market. These amendments are briefly reviewed in this article. In addition, a proposed amendment to the Basic Conditions of Employment Amendment Act that could impact on employers and the main features of the newly proposed Road Accident Benefit Scheme Bill that will replace the Road Accident Fund Act are considered. The latter Bill will introduce a no-fault system for road accidents as well as a simpler and more efficient claims administration process.

ETHICAL RULES AMENDED

The HPCSA has amended its general Ethical Rules on 1 March 2013. Ethical Rule 3(2) prohibits practitioners from canvassing or touting for patients either by themselves or through any other means. The definitions of "canvassing" and "touting" have now been expanded to include additional forms of conduct that will be impermissible. The amendments are as follows (changes underlined):

Ethical Rule 4(1) specifies the information that may appear on professional stationery. Previously practitioners were restricted to only include the information specified in the Rule on their stationery. This restriction has now been removed by deleting the word "only" in the old rule as follows:

OLD RULE

(1) A practitioner shall print or have printed on letterheads, account forms and electronic stationery information pertaining only to such practitioner's

(a) Name;

(b) Profession;

(c) Registered category;

(d) Speciality or subspeciality or field of professional practice (if any);

(e) Registered qualifications or other academic qualifications or honorary degrees in abbreviated form;

(f) Registration number;

(g) Addresses (including e-mail address);

(h) Telephone and fax numbers;

(i) Practice or consultation hours;

(j) Practice code number; and

(k) Dispensing license number (if any).

NEW RULE

(1) A practitioner shall print or have printed on letterheads, account forms and electronic stationery information pertaining to such practitioner's

(a) Name;

(b) Profession;

(c) Registered category;

(d) Speciality or subspeciality or field of professional practice (if any);

(e) Registered qualifications or other academic qualifications or honorary degrees in abbreviated form;

(f) Registration number;

(g) Addresses (including e-mail address);

(h) Telephone and fax numbers;

(i) Practice or consultation hours;

(j) Practice code number; and

(k) Dispensing license number (if any).

COMPETITION ACT: HEALTH CARE MARKET INQUIRY

The section in the Competition Amendment Act that would allow the Competition Commission to conduct market inquiries was implemented on 1 April 2013. This authorises the Commission to conduct a market inquiry if it had reason to believe that any feature of a market for any goods or services prevented, distorted or restricted competition in that market or to achieve the purposes of the Competition Act. Market inquiries had to be announced in the Government Gazette at least 20 business days before the commencement of such an inquiry. The notice in the Gazette had to indicate the terms of reference for the market inquiry and invite members of the public to provide information to the inquiry. It was widely accepted that one of the first market inquiries would be done in the health care industry especially in relation to pricing and the restriction of competition. The notice for such an inquiry has, however, not been gazetted to date.

BASIC CONDITIONS OF EMPLOYMENT AMENDMENT BILL

The Parliamentary Portfolio Committee on Labour has recently adopted the Basic Conditions of Employment Amendment Bill. Section 33A that was aimed at prohibiting employers from requiring their employees to purchase certain designated services, goods and products except under certain specified conditions was amended by the Portfolio Committee as follows:

"(1) An employer must not

(a) Require or accept any payment by or on behalf of an employee or potential employee in respect of the employment of, or the allocation of work to, any employee; or

(b) Require an employee or potential employee to purchase any goods, products or services from the employer or from any business person nominated by the employer.

(2) Subsection 1(b) does not preclude a provision in a contract of employment or collective agreement in terms of which an employee is required to participate in a scheme involving the purchase of specific goods, products or services, if the purchase is not prohibited by any statute and

OLD DEFINITION		NEW DEFINITION	
Canvassing	"Canvassing" means conduct which draws attention, either verbally or by means of printed or electronic media, to one's personal qualities, superior knowledge, quality of service, professional guarantees or best practice.	Canvassing	"Canvassing" means conduct which involves direct contact with prospective clients verbally or by, inter alia, distributing letters, pamphlets, circulars or other means of communication including printed or electronic communication, in which attention is drawn to one's personal qualities, superior knowledge, quality of service, professional guarantees or best practice in order to secure the prospective clients' custom.
Touting	"Touting" means conduct which draws attention, either verbally or by means of printed or electronic media, to one's offers, guarantees or material benefits that do not fall in the categories of professional services or items, but are linked to the rendering of a professional service or designed to entice the public to the professional practice.	Touting	"Touting" means, but is not limited to, conduct which draws attention, either verbally or by means of printed or electronic media, to one's offers, guarantees or material benefits that do not fall in the categories of professional services or items, but are linked to the rendering of a professional service or designed to entice the public to the professional practice.

(a) The employee receives a financial benefit from participating in the scheme; or

(b) The price of any goods, products of services provided through the scheme is fair and reasonable."

This amendment entails that an employer could for example require an employee to belong to a specific medical scheme as a condition of employment provided that it was not prohibited by law and the employee received a financial benefit from participating in the scheme or the price (medical scheme contribution) was fair and reasonable. This amendment still had to be approved by the National Assembly and the National Council for Provinces. When passed into law, section 33A would need to be considered by employers in the context of requiring employees to belong to designated medical schemes as conditions of employment.

ROAD ACCIDENT BENEFIT SCHEME BILL

The Road Accident Benefit Scheme Bill, 2013 that would replace the Road Accident Fund Act 56 of 1996 was recently published for comment. The Bill was intended to address the following needs:

- Replacement of the fault-based system underpinning the Road Accident Fund Act, which was not achieving its purpose effectively, with a system of no-fault;
- An effective benefit system, which
  - Was reasonable, equitable, affordable and sustainable in the long-term;
  - Optimised limited resources and facilitated timely and appropriate health care and rehabilitation to lessen the impact of injuries; and
  - Provided financial support to reduce the income vulnerability of persons affected by injury or death from road accidents;
- Simplification of claims procedures, reduction in disputes and the creation of certainty by providing defined and structured benefits; and
- The establishment of administrative procedures for the expeditious resolution of disputes to alleviate the burden on the courts.

The Bill provides for benefits in respect of road accidents to be paid on a no-fault basis. This means that accident victims would qualify for benefits regardless of who caused the accident and benefits would not be reduced based on the victim's contributory negligence. The current Road Accident Fund (RAF) would be replaced by a new administrator, the Road Accident Benefit Scheme Administrator (RABSA). RABSA would be funded from a levy provided for in the Customs and Excise Act 91 of 1964 and money would be appropriated by parliament for dealing with claims that arose under the Road Accident Fund Act.

Benefits

RABSA would only be liable for the payment of health care services received and medical reports compiled in the Republic of SA. The health care services to be covered were:

- Reparation or replacement of mobility aids, orthotic and prosthetic devices used by injured persons, which were damaged or destroyed in road accidents; and
- Health care services reasonably required for the treatment and rehabilitation of injured persons, including:
  - Pre-hospital care and inter-facility transfer;
  - Emergency and acute care;
  - Hospitalisation and out-patient services;
  - Rehabilitative care;
  - Vocational training;
  - Long-term personal care;
  - Orthotic and prosthetic devices and mobility aids; and
  - Structural changes to homes, vehicles and the workplace.

Preferred Providers

RABSA would be able to enter into agreements with public and private health care service providers to provide for the delivery of health care services to injured persons, the preparation of medical reports as well as the reparation or replacement of mobility aids, orthotic and prosthetic devices at agreed fees. RABSA could also require providers to adhere to policies, protocols or standards as well as obtain pre-approval (pre-authorisation) in respect of non-emergency health care services.

RABSA would only be liable for payment of the costs of health care services to a non-contracted health care service provider or a person who paid such a service provider at the tariff prescribed by the Minister of Transport if a claim was submitted and if the service was pre-authorised, if required. If no tariff was prescribed, the liability of RABSA would be limited to the reasonable and necessary costs of the health care service, aid or device or the medical report. In the case of a health care service, the service would be considered necessary if it was

- For the purpose of restoring the injured person's health to the extent practicable;
- Appropriate and of the quality required for that purpose;
- Performed only on the number of occasions necessary for that purpose;
- Given at a time or place appropriate for that purpose;
- Of a type normally provided by a health care service provider; and
- Provided by a health care service provider who was qualified to provide and who normally provided that health care service.

Future Health Care Services

RABSA could require that future health care services should be provided to beneficiaries in terms of individual treatment or rehabilitation plans. RABSA could require that the health care services required under the plan had to be provided by a contracted health care service provider or another service provider appointed for this purpose. RABSA's liability for payment would be limited to the health care services provided for in the plan.

CONCLUSION

Health care practitioners (HCPs) should consider the impact of the changes to the Ethical Rules and the changes or proposed changes to legislation on their practices and align their business practices accordingly, if indicated. This might entail ceasing practices that could be construed as canvassing and touting for patients. Once the Road Accident Benefit Scheme Bill was enacted, which still involved a lengthy consultation and parliamentary process, HCPs should consider their involvement in terms of becoming contracted providers to RABSA or participating in the protocol and tariff processes related to their practice.

References:
1. Basic Conditions of Employment Amendment Bill B15-2012 as amended by the Portfolio Committee on Labour (National Assembly).
2. Competition Act 89 of 1998.
3. Ethical Rules of Conduct for Practitioners registered under the Health Professions Act, 1974, GNR.717 of 4 August 2006 as amended by Government Notice R. 68 Government Gazette 31825 dated 2 February 2009 and Board Notice 26 of 2013 Government Gazette 36183 dated 1 March 2013.
4. Road Accident Benefit Scheme Bill, 2013. Notice 98 of 2013 Government Gazette 36138 of 8 February 2013.

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STEP 1: Go to www.medspec.co.za STEP 2: Click on the CPD Questionnaire button. STEP 3: Register or login if an existing user. STEP 4: Click on the MEDISCAN NEW IN CRITICAL CARE Programme button. STEP 5: Click on the questionnaire which you would like to complete, once completed click submit.

4 MODULES WILL BE AVAILABLE FOR 2014. 2 POINTS PER ISSUE HAVE BEEN APPLIED FOR. QUESTIONNAIRES WILL BE AVAILABLE ONLINE UNTIL 31ST JANUARY 2015. CERTIFICATES WILL BE E-MAILED IN FEB 2015.

ETHICS QUESTIONNAIRE

QUESTIONS		TRUE	FALSE
1	According to the new definition, *"Canvassing"* includes giving professional guarantees in order to secure the prospective clients' custom.		
2	In terms of the Competition Amendment Act, market inquiries by the Competition Commission have to be announced in the Government Gazette at least 20 business days before the commencement of such an inquiry.		
3	A market inquiry into the health care industry was announced in March 2013.		
4	In terms of the Basic Conditions of Employment Amendment Bill, an employer must not require a potential employee to purchase any goods from the employer.		
5	In terms of the Road Accident Benefit Scheme Bill (2013), accident victims may only make a claim if they did not cause the accident through their own negligence.		
6	In terms of the Road Accident Benefit Scheme Bill (2013), accident victims may not make claims based on medical reports compiled outside of South Africa.		
7	In terms of the Road Accident Benefit Scheme Bill (2013), an accident victim may not make a claim for replacement of a damaged prosthetic leg.		
8	In order to avoid corruption, the Road Accident Benefit Scheme Administrator (RABSA) is not allowed to enter into agreements with health care providers, but it may refuse to pay if there is suspicion of over-charging.		
9	RABSA could require providers to obtain pre-approval in respect of non-emergency health care services.		
10	It is illegal for RABSA to contract health care providers.		

Surname: _____ **Initials:** _____ **Title:** _____

MP: (YOUR HPCSA REGISTRATION NO.): _____

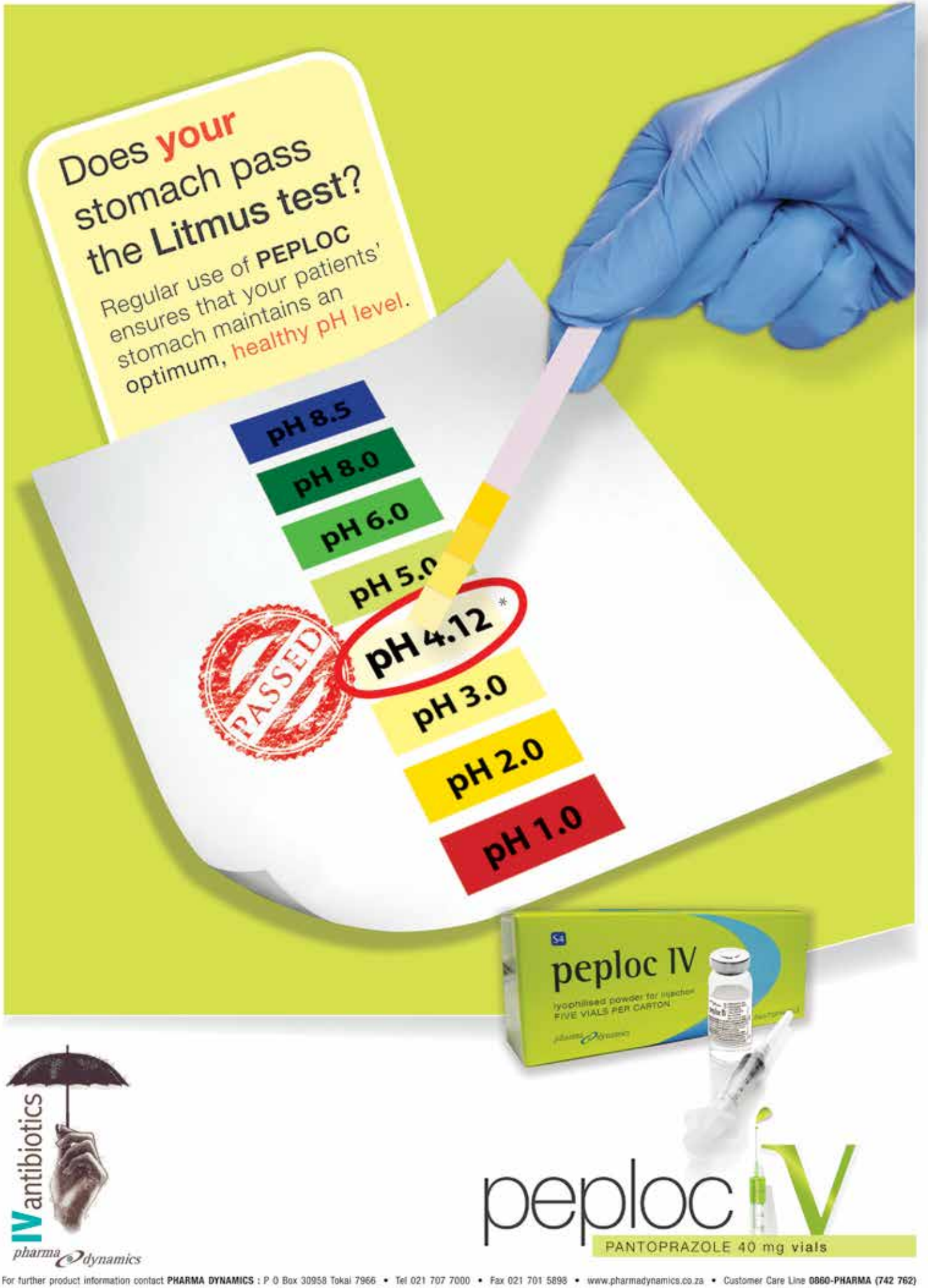
Address: _____

_____ **Code:** _____

Telephone: _____ **Fax:** _____

E-mail: _____ **Signature:** _____

INSTRUCTIONS: 1. Read the newsletter to find the answers. 2. Insert an X in the appropriate block. 3. Keep a photocopy for your records. 4. Place form in a sealed envelope and post to:- MedSpec Publishing, Private Bag X1036. Lyttelton 0140 or fax to 086 561 5122. Subscribe to qualify for CPD points.



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* USPDI, Volume 1 2007, 27th Edition, pg 2267.

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