NEWS

GENERICS PRICES IN SA COMPARE WELL WITH THOSE IN OTHER COUNTRIES

Prices of generic medicines in South Africa at ex the manufacturer level compare favourably with international prices and, in many instances, are priced lower than their counterparts in other markets. In fact, the average prices of 38 out of 42 generic medicines sold in South Africa were lower than the comparable price in a 7-country average.

This was the conclusion of an independent study on a basket of 42 generic molecules with the highest value in terms of consumption, and the generics with the greatest number of competing products in the South African private and public sector markets.

In 26% (11 out of 42 molecules), the average, ex manufacturer price in South Africa was lower than prices for the same molecule in all 7 countries in the study. The South African weighted average price was also the second and third least expensive in 21% (9 molecules) and 23% (10 molecules) respectively of the sample. The price was higher than the 7-country average in only 4 molecules. In only one instance, the South African generic was the most expensive.

The study compared ex manufacturer prices in South Africa with comparative weighted average prices for both the public and private sectors in Australia, Brazil, Canada, Germany, the Netherlands, the UK and the USA. Several criteria were used in the selection of the markets for the study, which included similarity in manufacturing standards, regulation and economies.

Every effort was made to adjust for differences between countries to ensure accurate comparisons. Prices used were based on identical strengths of the active ingredients and similar pack sizes but prices were based per counting unit (per tablet, per capsule). Prices in all markets were measured in US dollars.

Prices in all markets included discounts. This was because IMS reflects its prices at the gross selling price. The study was undertaken for the 4th quarter of 2003, prior to the introduction of the single exit price (SEP), in line with the Department of Health's requirement for a comparison before the introduction of the SEP.

'If we were to have undertaken the study post-SEP, it would not have been comparable because discounts would have been taken out of the South African prices. In fact, South African prices ex the manufacturer are even lower since the implementation of SEP because manufacturers have had to move from a gross to a net price following the removal of discounts in terms of the SEP legislation. The latter has resulted in a significant decline of the value of the total generics market', said Muhammad Bodhania, Chairman of the National Association of Pharmaceutical Manufacturers (NAPM).

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DOSE SPARING WITH INTRADERMAL INJECTION OF INFLUENZA VACCINE

The loss of half the US supply of influenza vaccine owing to contamination has created a critical shortage. Dose-sparing strategies that use intradermal delivery of vaccines may be one approach to consider. Intradermal injection of a fraction of the dose of commercial influenza vaccine would be a highly desirable dose-sparing strategy if it was found to be as immunogenic as a full-dose intramuscular injection.

In order to compare the immunogenicity and safety of intradermal immunisation with influenza vaccine with standard intramuscular immunisation, a randomised, open-label trial was conducted outside the influenza season in 100 healthy adults 18 - 40 years of age. Subjects were randomly assigned to receive either a single intramuscular dose of 0.5 ml of trivalent influenza vaccine, containing at least 15 μg of haemagglutinin per strain, by means of a prefilled syringe or a single intradermal dose of 0.1 ml, containing at least 3 μg of haemagglutinin per strain, by means of a fine-gauge needle; both injections were in the deltoid region.

The results showed that subjects who received an intradermal injection with one-fifth the standard dose of influenza vaccine had increases in the geometric mean HAI titre by a factor of 15.2 for the H1N1 strain in the vaccine, 19.0 for the H3N2 strain, and 12.4 for the B strain on day 21, as compared with respective increases by a factor of 14.9, 7.1, and 15.3 for the intramuscular injection of the standard dose.

Seroconversion and seroprotection rates were similar in the two groups on day 21, ranging from 66 to 82% and from 84 to 100%, respectively. Local reactions were significantly more frequent among recipients of intradermal injections than among recipients of intramuscular injections, but such reactions were mild and transient.

The researchers concluded that in this study group intradermal administration of one-fifth the standard intramuscular dose of an influenza vaccine elicited immunogenicity similar to or better than that elicited by intramuscular injection. Intradermal administration could be used to expand the supplies of influenza vaccine, but further studies are needed before this strategy can be recommended for routine use.

It is possible, however, that results similar to ours would not be seen in other populations, such as elderly persons, young

children, or those with underlying medical conditions. In addition, vaccines from other manufacturers may behave differently. Our study was limited to healthy young adults, was conducted in central Europe, and used one supplier's vaccine from a single year.

Further work is needed to demonstrate the wide-ranging relevance of reduced-dose intradermal injection of influenza vaccine before this approach can be recommended for routine use. Such studies are urgently needed to provide options for expanding the use of annual influenza supplies as well as to prepare for pandemic influenza.

The dense population of first-line immune cells (dendritic cells) suggests that the skin is an ideal target for the delivery of vaccine antigen. Our data reinforce the assertion that the immune system of the skin is a feasible and practical target and suggest that the relative immunogenicity of intradermal administration of influenza vaccine should at least equal that of intramuscular injection. This finding points to the viability of a dose-sparing strategy involving intradermal injection with a fraction of the intramuscular dose.

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NICOTINIC ACID AND HDL-C REDUCTION

It is well documented that modification of blood lipid concentrations significantly reduces the risk of fatal and non-fatal cardiovascular events in at-risk patients. Most studies have focused on low-density lipoprotein cholesterol (LDL-C) and the lipid-modifying intervention has relied solely on statins. These studies have consistently shown that LDL-C reduction with a statin reduces the risk of cardiovascular events by 25 - 30% irrespective of age, gender, baseline LDL-C or other risk factors of the treated population. Statins have thus become the foundation of lipid management and have been universally incorporated into national and international treatment guidelines.

Other studies have shown that even with reducing LDL-C to 2.6 mmol/l, at-risk patients retain a residual risk for coronary heart disease (CHD) events in the following 5 years, which remains unacceptably high. Researchers and clinicians are therefore looking beyond LDL-C reduction alone to re-evaluate the benefits of modifying other lipids, particularly HDL-C and triglycerides.

There is strong and consistent evidence from epidemiological studies to show that low HDL-C is an independent risk factor for CHD. These studies also demonstrate that the risk associated with low HDL-C occurs at all levels of LDL-C and serum triglycerides.

There is a consensus that an HDL-C concentration of > 1.0 mmol/l should be achieved in patients with established CHD, although recent guidelines suggest that the HDL-C target should be even higher in women (> 1.3 mmol/l). In individuals with additional risk factors, particularly type 2 diabetes or features of the metabolic syndrome, e.g. obesity with increased fasting insulin levels, the goal remains > 1.0 mmol/l.

Additionally, the Familial Atherosclerosis Treatment Study (FATS) and the Coronary Drug Project (CDP) have shown that nicotinic acid significantly increases HDL-C and reduces triglycerides. In the CDP, nicotinic acid resulted in significant reduction in mortality and morbidity versus placebo.

It is therefore logical to consider the benefits of combining nicotinic acid with a statin. This strategy has now been evaluated in a number of studies such as the HDL-Atherosclerosis Treatment Study (HATS) which clearly showed that patients receiving the combination of nicotinic acid plus the statin have a significantly reduced risk of cardiovascular and cerebrovascular disease.

Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) is the first randomised, controlled study to evaluate the effect of treatment with prolonged-release nicotinic acid in addition to statin therapy on atherosclerosis, as assessed by carotid intima-media thickness (IMT).

The 200 enrolled patients were randomly allocated to treatment with either prolonged-release nicotinic acid plus statin, or placebo plus statin for 12 months. The combination slowed the progression of atherosclerosis by 68%. There was also a 60% reduction in cardiovascular events.

The prolonged-release nicotinic acid formulation prescribed at a moderate dose of 1 000 mg nightly raised HDL-C by 21% and significantly reduced triglycerides compared with statin plus placebo. For years, large studies have shown that statins lower the risk of heart attacks and stroke by 30%. However, the remaining risk of 70% has proved very difficult to reduce. Now, by raising HDL-C, cardiologists said it might be possible to lower risk even more.

The only significant difference in tolerability was in flushing – a known side effect of prolonged-release nicotinic acid which occurred in most patients. However, adherence was the same in both groups.

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VIRTUAL REALITY TRAINING FOR CARDIOVASCULAR MEDICINE

Historically, physicians have learned new procedures by first practising on animals, cadavers or mechanical models,

eventually receiving 'on-the-job training' by operating on patients under the guidance of experienced teachers. However, in a commentary published in the 21 December 2004 issue of the *Journal of the American Medical Association (JAMA),* Emory Heart Center cardiologist Christopher Cates, MD, and Anthony Gallagher, PhD, Experimental Psychologist for the Division of Cardiology at Emory University Hospital, say this paradigm needs to change – especially in the field of cardiovascular medicine.

They point out that the rapidly expanding application of carotid stenting, which was approved by the US Food and Drug Administration (FDA) in September as an alternative to carotid endarterectomy, has brought to the forefront challenges involved in training physicians to perform these procedures. They believe that virtual reality (VR) training is a better, faster and safer way for physicians to learn endovascular procedures.

'Carotid stenting is an exciting new technology which certainly offers high-risk patients a less invasive option with significantly fewer bad outcomes (heart attack, stroke and death) when compared to carotid endarterectomy', says Dr Cates. 'However, unlike surgery, carotid stenting makes the physician's job more difficult because you can't see and feel tissues directly. Learning the hand-eye coordination of instruments, catheters and guide wires are sometimes more complex, requiring different new skills for physicians to develop.'

To help overcome these difficulties, Drs Cates and Gallagher designed one of the first VR programmes to train physicians in carotid stenting. Using simulators that look like human mannequins, physicians thread a catheter through an artificial circulatory system and view angiograms of the 'patient', while measuring the ability of doctors to perform the tasks instead of practising on patients. Emory has already trained over 103 physicians in carotid angiography using this VR technique.

In the *JAMA* commentary, the Emory researchers point out that if an embolus of thrombotic plaque is loosened and enters the brain during a carotid stenting procedure, the patient could have a stroke or die. 'That makes the risk conferred on the patient from the physicians' traditional learning curve unacceptable – and makes VR the training method of choice for this procedure', Dr Cates emphasises. 'With VR, physicians can receive objective feedback on their performances during and after completion of simulated cases. That means trainees can be required to reach specific proficiency levels before ever doing an endovascular procedure on a patient.'

GLAXOSMITHKLINE RECEIVES EUROPEAN APPROVAL FOR KIVEXA

GlaxoSmithKline (GSK) announced that it has received marketing approval from the European Commission for Kivexa, a new HIV medication. Kivexa combines two antiretrovirals (ARVs) in one tablet dosed once a day with no food or fluid requirements. Kivexa comprises two widely used nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine (3TC) and abacavir sulfate (ABC), for the treatment of HIV infection in combination with other ARV medications in adults and adolescents from 12 years of age. Kivexa is administered as one pill, once daily as the backbone of a combination treatment regimen.

Studies have shown that patients are more likely to adhere to their antiretroviral medication if they have to take fewer pills less frequently and if there are no food restrictions.

Kivexa provides potent and durable virological control and is compatible with multiple recommended third agents, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and boosted protease inhibitors (PIs). In treatment-naïve patients, Kivexa is associated with a low risk of cross-resistance with other NRTIs, thus helping preserve future treatment options.

The components of the Kivexa tablet have proven efficacy and safety profiles, as well as a favourable resistance profile. Lamivudine and abacavir sulfate have no known pharmacokinetic interactions with PIs or NNRTIs; therefore, Kivexa can be combined with PIs or NNRTIs. The components have each been well studied in both once- and twice-daily dosing regimens and in multiple combinations with other classes of ARV drugs. In clinical trials, Kivexa has demonstrated its ability to reduce the concentrations of HIV in plasma in both ARV treatment-naïve and experienced patients. Clinical trials have demonstrated the use of 3TC and ABC in more than 5 800 patients as a dual-NRTI backbone of multi-drug HIV regimens. Current experience with the two components includes more than 509 000 patient years' experience with regimens containing ABC and 2.6 million patient years with regimens containing 3TC.

- Sustained virological response was demonstrated over 120 weeks with ABC + 3TC twice daily in the SOLO/APV30005 study with 75% of patients who rolled over from the SOLO study, achieving a plasma HIV-1 RNA of " 400 copies/ml of blood at this time point.
- In a multi-centre, double-blind, controlled study (CAL30021, ZODIAC) in 770 adult patients, comparable efficacy and tolerability were demonstrated after 48 weeks between ABC dosed 300 mg twice daily and 600 mg once daily, when given in combination with 3TC 300 mg once daily and efavirenz (EFV) 600 mg once daily.
- Virological failure in clinical trials with treatment-naïve subjects receiving ABC/3TC/EFV first-line therapy was infrequent.
- A low rate of lipoatrophy was observed over 120 weeks with the ABC + 3TC backbone. Abacavir hypersensitivity reactions (HSR) were reported in approximately 5% of

patients across all abacavir clinical trials. In clinical trials using an abacavir once-daily regimen, the reported rate of HSR remained within the range recorded for abacavir given twice daily. The hypersensitivity reaction is characterised by fever, rash, gastrointestinal symptoms such as nausea, vomiting, diarrhoea or abdominal pain, symptoms such as generalised malaise, fatigue or achiness and/or respiratory symptoms such as dyspnoea, pharyngitis or cough. Symptoms of this reaction usually occur within the first 6 weeks of treatment although these reactions can occur at any time during therapy.

FDA ISSUES PUBLIC HEALTH ADVISORY RECOMMENDING LIMITED USE OF COX-2 INHIBITORS

Selective agents

The US Food and Drug Administration (FDA) has issued a Public Health Advisory summarising the agency's recent recommendations concerning the use of non-steroidal anti-inflammatory drug products (NSAIDs), including those known as COX-2-selective agents. The public health advisory is an interim measure, pending further review of data that continue to be collected.

In addition, the FDA announced that it is requiring evaluation of all prevention studies that involve the COX-2-selective agents Celebrex (celecoxib) and Bextra (valdecoxib) to ensure that adequate precautions are implemented in the studies and that local Institutional Review Boards re-evaluate them in light of the new evidence that these drugs may increase the risk of heart attack and stroke.

The FDA is issuing an advisory because of recently released data from controlled clinical trials showing that the COX-2-selective agents (Vioxx, Celebrex, and Bextra) may be associated with an increased risk of serious cardiovascular events (heart attack and stroke), especially when they are used in the long term or in very high-risk settings (immediately after heart surgery).

Also, the FDA has announced that preliminary results from a long-term clinical trial (up to 3 years) suggest that long-term use of a non-selective NSAID, naproxen (sold as Aleve, Naprosyn and other trade names and generic products), may be associated with an increased cardiovascular (CV) risk compared with placebo. Although the results of these studies are preliminary and conflict with other data from studies of the same drugs, the FDA is making the following interim recommendations:

- Physicians prescribing Celebrex (celecoxib) or Bextra (valdecoxib) should consider this emerging information when weighing the benefits against risks for individual patients.
- Patients who are at a high risk of gastrointestinal (GI) bleeding, have a history of intolerance to non-selective NSAIDs, or are not doing well on non-selective NSAIDs, may be appropriate candidates for COX-2-selective agents.
- Individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.

Consumers are advised that all over-the-counter (OTC) pain medications, including NSAIDs, should be used in strict accordance with the label directions. If use of an (OTC) NSAID is needed for longer than 10 days, a physician should be consulted.

Non-selective NSAIDs are widely used in both OTC and prescription settings. As prescription drugs, many are approved for short-term use in the treatment of pain and primary dysmenorrhoea (menstrual discomfort) and for longer-term use to treat the signs and symptoms of osteoarthritis and rheumatoid arthritis. The FDA has previously posted extensive NSAID medication information at **http://www.fda.gov/cder/drug/analgesics/default.htm**.

The FDA is collecting and will be analysing all available information from the most recent studies of Vioxx, Celebrex, Bextra, and naproxen, and other data for COX-2-selective and non-selective NSAID products, to determine whether additional regulatory action is needed. An advisory committee meeting is planned for February 2005, which will provide for a full public discussion of these issues.

The FDA urges health care providers and patients to report adverse event information to FDA via the MedWatch programme: tel 1-800-FDA-1088, fax 1-800-FDA-0178, or Internet **http://www.fda.gov/medwatch/index.html**.

The Public Health Advisory is available online at **www.fda.gov/cder/drug/advisory/nsaids.htm**.

PRACTICE MANAGEMENT

FINANCIAL MANAGEMENT – PART II

Note: The following words are interchangeable throughout the course: firm, business, organisation, company and practice; product and service; customer, client and patient.

Sources of capital

Clearly the different sources of capital have different risk and cost implications. Share capital and accumulated profits are permanent sources of capital provided at no cost to the business, while loans from an external source are repayable, and carry interest. This is referred to as 'gearing', which simply means the amount of money that is borrowed and that bears interest. The more money you owe to a bank the higher the risk of your company is and the higher your gearing is.