NEWS

MEDICINES PRICING SINGLED OUT

Medicines pricing came under scrutiny at Mx Health's Quarterly Healthcare Review on 23 March when a broad range of industry players spoke frankly about their concerns around what chair Partricia Glyn referred to as a 'sword of Damocles' — the single-exit pricing regulations due to come into effect on 2 May and widely predicted to cause chaos if implemented as proposed. (Sadly Government was not represented on the panel — because of practical problems, not because they didn't want to attend, but it did leave a gap.)

The panel recognised that Government has been banging on the industry doors for years and now has no choice but to (as Glyn put it) 'bury the carrots and bring out the sticks'. General agreement with certain principles of the proposed regulations, such as the need for transparency, were countered by major concerns voiced by many panel members, notably with the uncompromising 50% reduction in the price of medicines, which appears to have been a shock to almost all.

Vicki Ehrich (Pharmaceutical Manufacturers' Association), representing the multinationals, said that the PMA is committed to the objectives of the legislation and wishes to be a partner. However, her organisation has serious problems with the 50% price cut, which will disadvantage some companies unfairly. Kurt Worrall-Clare (legal advisor to the Hospitals' Association of South Africa) said that HASA supported key fundamentals of the legislation but urged a broader approach to reducing health care costs and warned that if the regulations are not reworked to include the private hospitals, HASA might be forced to take legal action.

Major concerns with practicalities were voiced by Tony Lloyd, CEO of Alpha Pharm and representing pharmaceutical wholesalers (which he referred to as 'the ham in the sandwich'), while Jackie Shevel of Netcare questioned the whole principle of superregulation and whether it actually works. Accusing Government of arrogance, a dismissive attitude and lack of clarity, he nevertheless accepted that the industry needs to take an active role in looking for a policy that will work for all South Africans.

The free market system came in for tough criticism from the remaining two members of the panel. SAMA's Kgosi Letlape said the Association 'would like to see professionalism replace profiteering' and stressed that Government's responsibility is to the whole of society. Susan Mynhardt of Mx Health embroidered on this, pointing out that 'medicine costs have gone ballistic', querying whether the regulations would be as devastating as predicted ('We have heard that the multinationals will just go away ... I don't believe that, I believe strongly in their creativity'), and motivating the industry to work together to bring health care costs down.

In closing, Neels Barendrecht of Mx Health also had strong words for the industry, which he said 'has had a free market system for a long time now, and what has it left us with? No more than 7 million people covered for health care. Health is a social responsibility, and we as an industry need to make creative, constructive input.'

Trenchant quotes from the panel:

Vicki Ehrich

'The original products of today are the generics of tomorrow.'

Kurt Worrall-Clare

'The legislation makes serious inroads into constitutional rights such as free trade.'

Tony Lloyd

'If the pharmacist is unsustainable, then we are too.'

'This is a poor industry. This is not an industry that people are clamouring to get into.'

Jackie Shevel

'There are similar regulations worldwide but nothing as draconian as this. And they haven't worked.'

Kgosi Letlape

'Maybe it's time for a sandwich without ham.'

Susan Mynhardt

'There is no freedom without responsibility.'

Emma Buchanan

RISK OF ARCHIVED RESISTANCE AFTER INTRAPARTUM NEVIRAPINE

Question: A woman from an African country received single-dose intrapartum nevirapine for prevention of mother-to-child HIV transmission 6 months ago. She now wishes to start HAART. A genotype test shows no NNRTI resistance mutations. Can we be sure she has no archived resistant virus? If she does, how would she respond to a regimen of nevirapine/zidovudine/lamivudine?

Response from Andrea Kovacs, MD, Associate Professor of Pediatrics & Pathology at the University of Southern California Medical School; Director of Comprehensive Maternal-Child HIV Management & Research Center; Head of Division of Pediatric Infectious Diseases at LAC+USC Medical Center.

You ask an excellent question for which we do have some information. Nevirapine recently has been used in 2 international studies (HIVNET 006 and 012), chosen for its remarkably long half-life and significant potency in rapidly decreasing HIV replication. The one drawback to this agent is the rapid emergence of resistance when it is used as a single agent; moreover, only a single mutation can confer a 100-fold decrease in viral susceptibility.

In these studies, women received 1 dose of oral nevirapine intrapartum (200 mg) and the newborn received 1 dose as well (2 mg/kg) within 72 hours of birth. Women had follow-up visits, and evaluations for resistance were done. In the HIVNET 006 study 3 of 15 women (20%) evaluated 6 weeks after their single dose of nevirapine had developed the K103N mutation that confers high-level resistance to nevirapine. In the second study, HIVNET 012, 21 of 111 women (19%) tested were found to have mutations that confer resistance to nevirapine at 6 - 8 weeks postpartum, with K103N again being the most common. By 12 - 24 months the mutations had disappeared in the 11 women who were tested. No difference in the rate of mutations was found between women who delivered HIV-infected or -uninfected infants. Resistance was associated with high viral load and low CD4+ cell count. Among the 24 HIV-infected infants tested, 46% had nevirapine resistance mutations, with Y181C the most common. As in the mothers, the mutations were no longer detected upon subsequent retesting. Among 9 infants who were found to be infected with HIV after 8 weeks, presumably through breast milk, only 1 had the K103N mutation.

In another study, PACTG 316, the same single-dose regimen was evaluated in women in the USA who were also receiving other antiretroviral agents. In this study, too, after a single dose of nevirapine 11% of 104 women with plasma HIV-1 RNA levels > 400 copies/ml were found to have nevirapine resistance.

These findings come as no surprise. Early studies demonstrated the rapid emergence of drug-resistant virus during monotherapy with nevirapine. The Y181C mutation, which was most commonly seen in the infants exposed to nevirapine in the HIVNET studies, was reported most often. For patients on longer-term therapy with nevirapine, the K103N mutation is more commonly selected, as was seen in the women in the HIVNET studies. It is thought that these mutations are present as minor variants within the viral quasispecies and thus can be selected for during therapy when other drugs are not present to completely and rapidly suppress replication. In the case of the pregnant women, the drug was found to have a long half-life (61 hours), and thus as the drug level decreases below the level that can completely suppress viral replication, new mutations can also occur.

The good news in all of this is that the mutants that are selected do disappear and wild-type virus repopulates and predominates. In theory, therefore, the reintroduction of nevirapine at delivery during a second pregnancy should result in suppression of HIV replication, because most of the viral variants will be sensitive; if the mutants do reappear, it will likely occur after delivery. With the addition of 2 new antiretroviral agents one would expect that HIV replication could be maximally suppressed and transmission may be prevented. (Nevirapine resistance mutations have been reported to persist, although, in patients who have had prolonged therapy, in contrast to what was reported among women treated with single-dose nevirapine.)

In terms of the question, even though no nevirapine resistance mutations have been detected 6 months after delivery, resistant variants may have developed in the postpartum period and may emerge as the predominant quasispecies once the patient is reintroduced to a nevirapine-containing antiretroviral regimen. However, as noted above, only 11 - 20% of women treated with single-dose nevirapine had resistance at 6 weeks postpartum, with the remainder having no detectable nevirapine resistance mutations. Close follow-up with frequent HIV-1 RNA levels during the first month of therapy would be helpful in making an early assessment of the efficacy of the proposed nevirapine/zidovudine/lamivudine regimen. Hopefully you will see a rapid decline in HIV-1 RNA to undetectable levels. If viral replication is not fully suppressed or if there is viral rebound, repeated genotypic testing during the new antiretroviral regimen would reveal these mutations. If other agents are available, therapy could then be readjusted.

RESEARCHERS DISCOVER FACTOR THAT KILLS CELLS AFTER BRAIN INJURY

Infusion of antibody for 7 days dramatically boosts nerve cell survival after brain injury

Dead and dying nerve cells directly affected by stroke, other injury, or neurodegenerative diseases like Alzheimer's are known to trigger cell death, or apoptosis, in their healthy neighbours. This cell death cascade is often more devastating than the original injury in terms of brain and spinal cord damage. But new evidence in an animal model suggests that these neurons could be saved.

Researchers from Weill Cornell Medical College, University of Texas Southwestern Medical Center, Ohio State University, and University of Saarland (Germany) report in the current online issue of Proceedings of the National Academy of Sciences (PNAS) that they were able to prevent the injury-induced death of cortical neurons in mice and rats by neutralising a specific protein called proNGF that cells in the injured brain secrete.

The researchers used an antibody to proNGF to prevent its interaction with another protein called p75 that is found on the surface of injured neurons, saving them from almost certain loss. This treatment boosted nerve cell survival to over 90% in injured rats compared with a 61 - 66% cell survival seen in rats not treated with the antibody.

While the antibody infusion used in the study is not appropriate for treatment of humans, the experiment published in PNAS validates proNGF as a viable target for discovering molecules that can be used to block proNGF in patients.

ProNGF is an unprocessed form of a nerve cell-protecting substance called NGF, or nerve growth factor. The study validated this target not only by showing that blocking proNGF prevents neuronal death, but by demonstrating that proNGF and the p75 receptor with which it interacts are upregulated after injury.

ProNGF is a molecule that is made in response to injury, when it is secreted by cells, and can be found outside the cell in the cerebrospinal fluid. P75 is a receptor that neurons upregulate following injury. This experiment indicates that if you give antibodies that block the binding of proNGFs to p75, you can prevent the death of neurons, at least in animal models.

If one could identify a compound that could pass the blood-brain barrier and impair the binding of proneurotrophin to cell receptors, then it could be a potential drug that could be tested in animals and eventually in patients, researchers said. The blood-brain barrier is a protective layer of cells that stops most compounds from entering the central nervous system — a problem that has to be overcome when finding drugs to treat brain conditions.

In the study, the researchers looked at injuries to the corticospinal tract, nerves that carry signals from the brain to motor nerves, which carry out movement. They are frequently damaged in strokes. Past studies have found that after such an injury, about 40% of corticospinal nerve cells die within 14 days.

Dr Klaus Giehl, who started this work at the University of Saarland in Hamburg, Germany, and completed it at the University of Texas Southwestern Medical Center at Dallas, led the study using a rigorous model of corticospinal injury in rats that he has developed. Cornell University has filed for patent protection on these findings and is actively seeking partners to develop new medicines based on the findings.

Source: **http://www.cornell.edu**

HRT MAY DAMAGE HEARING

Postmenopausal women who receive hormone replacement therapy may risk diminished hearing, suggest the results of a new study, presented at the annual meeting of the Association for Research in Otolaryngology.

The **NewScientist.com** news service reports that tests on 64 women over the age of 60 — half of whom were on HRT — showed that those taking HRT had 10 - 30% worse hearing than those not taking HRT. In addition, tests on how well the brain processes that information showed that those on HRT had their processing ability reduced by an average of 30%.

'This would be most noticeable in situations where there's a lot of background noise and information needs to be filtered and prioritised,' explains Robert Frisina of the National Technical Institute for the Deaf at Rochester Institute of Technology, who led the small pilot study. 'This type of hearing loss occurs naturally as a part of ageing, but it appears as if the ageing process, when it comes to hearing, was accelerated in these women,' he told New Scientist.

It is not understood why HRT might have this effect on hearing. Indeed, Frisina had expected the hormones to enhance hearing ability. Frisina speculates that water retention and electrolyte imbalance that occurs during the menstrual cycle may affect hearing.

Frisina cautions, 'It's (also) important to alert women that there could be another significant side-effect of HRT'. Balance problems — a leading cause of injury among the elderly — may also be a concern for women taking HRT.

But John Stevenson, from the British Menopause Society, is sceptical, saying that the study is too small to be conclusive. 'I would be very cautious in interpreting the results before a proper prospective large-scale study is carried out. If there really was a 30% difference in hearing ability in women who take HRT, then I think we would have been aware of it clinically — patients would have complained about it and clinicians would have reported it,' he told New Scientist.

POSITIVE RESULTS FOR EARLY EJACULATION PRODUCT

NexMed, Inc, has announced positive results from an international pilot study for NM100061, developed as a treatment for early ejaculation (EE).

EE, also known as premature ejaculation, is the most prevalent condition of all male sexual problems, and is defined as the absence of voluntary control over ejaculation, resulting in ejaculation either preceding vaginal entry or occurring immediately upon vaginal entry. According to the May 2001 issue of *Medical Aspects of Human Sexuality*, EE affects approximately 33% of men, and is most common in adolescents, young adults, and men who lack sexual experience and frequency. Currently no pharmaceutical product has been approved by the FDA to treat the condition.

The 3-month multicentre study was double-blind, placebo controlled and included a total of 89 patients. The patients in this study averaged 43 years of age and had been diagnosed with EE for 2.6 years. The primary endpoint for this trial was drug efficacy, as measured by simultaneously extending the ejaculatory latency time and improving the patients' overall sexual satisfaction ratio by a minimum of 20%.

The results of the study indicate that the primary endpoint was achieved, with a satisfaction rate for patients using the product being 84.8%, versus 23.3% in the placebo group ($p < 0.001$ compared with placebo). The adverse events

reported were local, mild and transient and, importantly, none of the enrolled patients reported numbness or decrease in penile sensations.

NexMed completed testing the product in three separate studies that included more than 170 patients. Dr Joseph Mo, President and CEO of NexMed stated, 'Results from the most recent study are encouraging, and remain consistent with our previous findings. We intend to apply for approval to the US Food and Drug Administration, and upon acceptance, begin clinical development in the United States.'

SEEKING A MECHANICAL SOLUTION TO TREATING EAR INFECTIONS

Each year, Americans spend $5 billion on ear infections. Doctors often prescribe two different antibiotics for the same infection. For more serious cases, they perform 500 000-plus myringotomies and grommet insertions annually. Nonetheless, about 20% of children have repeated episodes of ear infections that persist into adolescence and even adulthood. As is well-known, chronic infections can lead to loss of hearing and balance, as well as to more critical inner-ear infections.

As bacteria become resistant to existing drugs, researchers scramble to develop new antibiotics. But Samir Ghadiali, professor of mechanical engineering and mechanics at Lehigh University in Pennsylvania, USA, thinks there is a better way to tackle the problem. He is studying the biomechanical and biophysical properties that govern the Eustachian tube. 'The goal of our research is to identify the causes of Eustachian tube dysfunction, which we hope will lead to the development of novel therapies that target the underlying cause of middle-ear disease. If we can open the Eustachian tube,' he says, 'this will help prevent bacteria from accumulating and inflammation from occurring in the middle ear.'

One goal of Ghadiali's research is to answer a question that has long baffled doctors — why the Eustachian tube opens and closes easily in some people and not in others. Engineers, he says, can answer that question by modelling the functioning of a healthy Eustachian tube and using the model to predict the physical behaviour of a diseased tube.

'Until recently, researchers have visualised the ear's interior and speculated why the Eustachian tube does or does not open,' Ghadiali says. 'We are attempting to push past this limitation by taking imaging data from people who do not have ear infections and creating mathematical models. By going from the image to the model, we can simulate whether or not the tube will open and we can quantify certain parameters, such as how long the tube will stay open.'

Ghadiali also hopes to apply his models to each of the six or seven distinct 'patient populations' identified by doctors as having Eustachian tubes that, for differing reasons, resist opening: children from a few months to 2 years old, those aged 2 - 6, those aged 7 - 12, and teenagers, as well as patients who have undergone surgery for cleft-palate, another group which is prone to chronic infections.

SIMPLE PROGRAMME PREDICTS WHO IS MOST AT RISK OF BREAST CANCER

UK scientists have devised a user-friendly computer programme, called the IBIS risk evaluator, which can give the most accurate estimate yet of a woman's chance of developing breast cancer.

The programme, details of which are published in the current issue of *Statistics in Medicine* (Vol. 23, Issue 7), pulls together all the existing evidence on the causes and risk factors for breast cancer, such as age, family history and whether a woman has had children. The risk evaluator is already in use in a few hospitals.

To use the programme, a woman or her doctor answers questions on her family history of breast cancer — which of her relatives have been affected and at what age. This allows the programme to work out whether the woman is likely to carry a high-risk breast cancer gene, such as BRCA1 or 2, or whether she is likely to carry an as yet undiscovered lower risk gene. Further questions investigate a woman's personal risk factors, such as her age, if she has had children, her height and weight, whether she is postmenopausal and if she has taken HRT. Her replies are then factored into the equation to produce a personalised risk profile.

Because the risk of breast cancer increases with age, the programme gives a projected risk for the next 10 years as well as over the woman's lifetime. This risk is given as a percentage probability alongside the average risk for a woman of the same age in the UK. The majority of women can be reassured that their risk is similar to the population average.

Women who are at a high risk could join the IBIS-II prevention trial or be referred to a family cancer clinic. The IBIS-II prevention trial is a 10-year study involving 10 000 healthy women who are at an increased risk of breast cancer. Half of these women will be given a drug called anastrozole which has already been shown to be the most effective hormone treatment for breast cancer.

For all women, especially those at an increased risk, general advice can be given including guidance on weight loss, limiting HRT use and screening.

The concept is that the IBIS risk evaluator brings together everything known about the causes of breast cancer to predict a woman's individual risk. The developers believe it will help doctors to deal with the growing number of the 'worried well' who visit their GP seeking advice on how they can avoid illness. The programme was originally devised to help find high-risk women who could take part in Cancer Research UK's

breast cancer prevention trial, IBIS II. However, the researchers quickly realised that the programme had much wider potential.

Professor Jack Cuzick, Director of Cancer Research UK's Centre for Epidemiology, Mathematics and Statistics at Queen Mary, University of London, who led the research, explains: 'We hope to develop this tool further to include risk factors for a variety of common diseases including heart disease and other cancers. One day it might be available in every GP surgery, perhaps even in every shopping centre, so people can find out their personal risk of various diseases and get a print out of what they can do to reduce their risk.'

Source: **www.cancerresearchuk.org/**

NEVIRAPINE-INDUCED RESISTANCE IS A PROBLEM

Research findings presented at a recent meeting of the International AIDS Society have indicated that HIV resistance in response to nevirapine therapy is increasing. Nevirapine was used in two international studies (HIVNET 006 and 012). Single-dose nevirapine (NVP), given to the mother at onset of labour followed by a dose to the infant, is a low-cost and simple strategy to reduce mother-to-child transmission (MTCT) of HIV in resource-poor settings. However, early trial findings demonstrated NVP resistance was detected in 21/111 of women (19%) at 6 - 8 weeks and mutations were also detected in some women as early as 7 days following the 200 mg maternal dose. Samples taken within 2 weeks of receiving single-dose NVP harboured a high frequency of NNRTI resistance mutations. K103N is the predominant mutation selected at 8 weeks. The investigators noted: 'Further studies of NVP resistance in women and children receiving single-dose NVP may help optimise use of NVP for prevention of MTCT.'

Both studies confirm the well-recognised fact that single doses of nevirapine given to antiretroviral-naïve women will result in selection of resistant variants. The scale of this is startling. Three-quarters of the samples obtained from one trial 2 weeks after the dose was given had evidence of mutations. It also highlights how fast these mutations can disappear from the plasma, but although not present in later plasma samples they will be archived in pro-viral DNA.

Neither study addresses the crucial question of the longer-term consequences of briefly selecting out resistant virus. It has been argued that such variants arise by natural mutation every day in untreated, infected individuals. However, this is not the same as flooding the long-lived lymphoid cells and sanctuary sites, albeit briefly, by single-dose intervention. Will this result in loss of efficacy in future pregnancies, or for those women able to access treatment for themselves? First-line ART in many poorly resourced settings is with nevirapine-containing combinations, so this is not an academic question.

The good news in all of this is that the mutants that are selected do disappear and wild-type virus repopulates and predominates. In theory, therefore, the reintroduction of nevirapine at delivery during a second pregnancy should result in suppression of HIV replication, because most of the viral variants will be sensitive; if the mutants do reappear, it will likely occur after delivery. With the addition of 2 new antiretroviral agents one would expect that HIV replication could be maximally suppressed and transmission may be prevented.

FNS

PRACTICE MANAGEMENT

BUSINESS PLANNING PART VII

CONCLUSION

The use of appendices

This module emphasised the use of a business plan as a practice management tool. Where a business plan is developed for securing financial support, a need could exist for additional information to substantiate the business plan. Appendices can be used to supply this information. Examples of additional information could include the following:

Market surveys

Providing detailed information on the demographics of the practice, current customer base or future market:

- age
- income level
- gender
- payment methods
- geographical distribution.

Financial information

This will vary depending on the purpose of the business plan but could include:

- detailed budgets relating to the operational plan
- financial records of the past year such as balance sheets and income statements
- financial projections on future income and cash flow.