

# Society urged not to set rules for medicines displays

Two organisations representing pharmacy companies have told the Royal Pharmaceutical Society not to be prescriptive about how medicines are displayed for sale in pharmacies.

Both the National Pharmacy Association and the Company Chemists' Association say that ensuring the safe use of medicines by giving advice before they are bought is more important than whether they are on open display or available for self-selection.

In its response to a Society consultation on self-selection of pharmacy medicines, the CCA says that the Society should place restrictions on the way that P medicines are made accessible to the public, but that it should consider carefully whether it should be prescriptive over practical matters, such as the way medicines are displayed.

"We suggest that the Society considers how to ensure that patients and consumers receive appropriate advice and are enabled to purchase the medicines they need safely and effectively, rather than attempt to regulate how medicines are displayed," it says.

The CCA does not see allowing people to pick up packs of medicine as synonymous with self-selection if pharmacists or suitably trained staff are in a position to intervene before a sale takes place.

"Some might consider that it might be difficult to take medicines from patients if they are later thought to be unsuitable by the pharmacist, but we consider this to be a matter professionals will need to deal with themselves, rather than form part of a professional code," the CCA says.

CCA chief executive Rob Darracott commented: "Limiting self-selection is a low-tech way of ensuring the pharmacist can intervene. We recognise that the market will want to test different ways of presenting medicines to the public moving forward, but the key factor is maintaining the opportunity for professional intervention."

The NPA said that open display, rather than self-selection, is what its members want, but that there should be differentiation in the public eye between general sale list medicines and pharmacy medicines.



Providing advice is more important than whether medicines are on open display

"Patient safety needs to be maintained through intervention or advice from a member of the pharmacy team," said Michelle Styles, head of information at the NPA.

## NPA opposes reclassifying pseudoephedrine

Proposals to restrict pseudoephedrine and ephedrine to prescription supply in order to prevent methylamphetamine abuse becoming a problem in the UK are based on false grounds, the National Pharmacy Association has told a Parliamentary inquiry into the plan.

"Reclassification would deprive many people of a safe, effective medicine and there is no evidence that reclassification would reduce methylamphetamine use in the UK," the NPA says in a submission to the joint inquiry of the all-party parliamentary groups on drug misuse and on primary care and public health.

It adds that having to wait for GP appointments rather than being able to buy what they need from pharmacies would inconvenience patients.

The NPA also believes that there are no effective alternative decongestants to pseudoephedrine. It says: "Professor [Ron] Eccles, of the Common Cold Centre, stated in a recent review that phenylephrine is a poor substitute for pseudoephedrine as an orally administered decongestant as it is extensively metabolised in the gut and its efficacy as a decongestant is unproven."

In an eight-point response, the NPA addresses each of the concerns set out by the Medicines and Healthcare products Regulatory Agency in its proposal to remove the two drugs from the pharmacy category.

The association says:

- There is little evidence that pseudoephedrine and ephedrine are used in the UK to manufacture methylamphetamine

- Concern is based on events in countries where pseudoephedrine was previously available by self-selection in non-pharmacy outlets in packs of up to 250 tablets of higher strength than in the UK
- Only 10 per cent of illicit methylamphetamine manufactured in the US is sourced from OTC products, most of which are stolen
- Other countries dealt with the problem by introducing restrictions similar to pharmacy control in the UK
- Evidence from the US suggests that restricting pseudoephedrine supplies had no effect on amounts of methylamphetamine available for illicit use

Addressing other impacts, the NPA adds:

- Reclassification will reduce access to safe, effective medicines
- Many affected products are on the NHS blacklist
- Reclassification will drive up GP workload

The NPA's preferred solution to the risk of illicit conversion of pseudoephedrine to methylamphetamine is to restrict packs available for pharmacy sale to a total of 720mg of pseudoephedrine, to ask pharmacists to sell only one pack per patient and to monitor sales more closely, supported by professional guidance from the Royal Pharmaceutical Society.

The two all-party groups launched their inquiry in the light of the MHRA's proposal to make ephedrine and pseudoephedrine prescription products (*PJ*, 10 March, p269).

## Monitoring of P medicines sales needs to improve

The proposed reclassification of pseudoephedrine and ephedrine demonstrates that the monitoring of sales of pharmacy-only medicines needs to improve, Roger Walker, consultant in pharmaceutical public health at the National Public Health Service for Wales, says in a letter published this week.

Pharmacists believe the proposed reclassification has raised questions about their ability to supervise sales of P medicines, he says, but this could have been avoided. "Perhaps as a profession we should have acknowledged that there was a potential problem and reinforced the existing measures to demonstrate that our supervision was robust enough to protect public health," he writes.

Improving the supervision and monitoring of sales of P medicines could, he says, have deflected attention from the need for reclassification. "In the future we must ensure that we have a better system in place to protect the public from the misuse of over-the-counter medicines," he argues.

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### Society

#### Welsh support for pharmacy

The Welsh Directorate has welcomed support for the pharmacist's role from political parties in Wales (p469).

#### Annual review now available

The Society's annual review for 2006 has been published and is being distributed with this issue of *The Journal* (p470).

## MPs' committee slams NPfIT

Questions remain over the National Programme for IT and urgent action is needed at the highest level if the long-term interests of NHS patients and taxpayers are to be protected. So said Edward Leigh, chairman of the House of Commons Committee of Public Accounts, as it published a report this week into progress made by the Department of Health in implementing the programme.

"The programme is not looking good. The electronic patient clinical record, which is central to the project, is already running two years late. The suppliers are struggling to deliver. Scepticism is rife among the NHS clinicians whose commitment to the programme is essential to its success. And, four years down the line, the costs and benefits for the local NHS are unclear," he said.

However, the Government has defended the programme, saying that the PAC report is based on out-of-date information.

During its investigation the PAC examined the current status of the electronic patient record, the costs of the programme, the local management and implementation of systems within the NHS, the extent to which clinicians were involved in developing the systems, the management of suppliers and patient confidentiality.

The report makes several recommendations, including one that the DoH should seek to modify the procurement process so that secondary care trusts and others can, if they wish, select from a wider range of patient administration systems and clinical systems, provided these

conform to national standards. "This approach could have the benefit of speeding up the deployment of new systems and making it easier to secure the support of clinicians and managers," it says.

Commenting on the report, health minister Lord Hunt said: "This PAC report is based on a National Audit Office report [*PJ*, 24 June 2006, p741] that is now a year out of date. Since then substantial progress has been made and the NAO recommendations have already been acted on. Costs of the programme have not escalated. In fact, the NAO acknowledged that costs were under control and the strength of the contracts means that payment is not made until systems are delivered, which protects the taxpayer."

The DoH says that it will respond to the committee's full list of conclusions and recommendations in due course.

"Department of Health: The National Programme for IT in the NHS" is available in the Public Accounts Committee section of the UK Parliament website at [www.parliament.uk](http://www.parliament.uk) and via *PJ Online* ([www.pjonline.com/links/pj](http://www.pjonline.com/links/pj)).



Move from paper to electronic records is two years late

## Voice messaging to be built into dispensary system

Pharmacists will be able to generate automatic voicemail messages for patients to tell them their prescription is ready or to remind them of a medicines use review appointment following an agreement between Message Dynamics and Cegedim Rx.

Message Dynamics plans to integrate its messaging system with Cegedim Rx's Pharmacy Manager and Nexphase dispensary systems. This will allow voice messages to be left on both landline and mobile telephones, something Cegedim Rx believes will be useful when trying to contact older patients who may not use SMS text messaging. The messaging service is available in 47 languages and uses secure servers and PIN access so that patients can maintain their own telephone numbers, PIN, contact times and preferences.

Cegedim Rx believes this is the first time that a voice messaging capability has been incorporated into a dispensary system. Last year, Systems Solutions included the ability to send text messages, e-mails and letters in its QicScript pharmacy system (*PJ*, 23 September 2006, p358).

## Pharmacist pleads guilty to Society staff assault

Pharmacist Samuel Edwin Ashby faces a possible jail sentence after pleading guilty to assault causing actual bodily harm on being told that he was to be struck off the Register of Pharmaceutical Chemists.

Mr Ashby hit the Royal Pharmaceutical Society's interim head of professional conduct, Desmond Fitzpatrick, over the head with a 10-inch iron bar during a Statutory Committee hearing on 25 October 2006 (*PJ*, 28 October 2006, p503 and 9 December 2006, p718).

Sentencing was adjourned until 18 June, pending the preparation of probation and psychiatric reports.

Mr Ashby has appealed against being struck off and remains registered pending the outcome of his appeal.

## New NICE work programme announced

Clinical guidelines on eight further topics are to be produced by the National Institute for Health and Clinical Excellence.

The 14th wave of referrals to NICE by ministers at the Department of Health seeks guidance for the NHS on:

- Preventing venous thromboembolism in all medical patients admitted to hospitals
- Assessing and managing acute coronary syndromes in adults in primary and secondary care with symptoms of suspected recent onset or deteriorating coronary heart disease
- Investigating, assessing and managing acute chest pain of suspected cardiac origin
- Treating pregnant women who misuse drugs and/or alcohol and the management of their newborn babies

- Managing benign prostatic hyperplasia
- Diagnosing and treating constipation in children
- Recognising and treating neonatal jaundice
- Diagnosing and managing unknown primary tumours

□ **Appraisal review** NICE is reviewing the technology appraisal guide that sets out how it takes decisions on the use of new medicines and treatments in the NHS. The review is expected to last until October, after which a draft revised guide will be available for three months of public consultation.

NICE chief executive Andrew Dillon said: "This update will give our stakeholders the chance to tell us how they think our approach should evolve so that we can stay at the leading edge of this important work."

Access to *PJ Online* is free to all

### Letters to the Editor

Each week's *Pharmaceutical Journal* appears on *PJ Online* on Friday. However, the letters pages are available as a PDF file on Thursday. [www.pjonline.com](http://www.pjonline.com)

### Foreign medicines identification

A list of websites, recently updated, for identifying foreign products. [www.pjonline.com/pip](http://www.pjonline.com/pip)

# Consultation on POM to P naproxen switch launched

The number of medicines that women can buy over the counter to treat period pain may soon increase with the launch last week of a consultation on naproxen's switch from POM to P status.

The Medicines and Healthcare products Regulatory Agency is consulting on whether naproxen should be made available from pharmacies for the treatment of primary dysmenorrhoea for women aged between 15 and 50 years. It is estimated that 40 to 70 per cent of women of reproductive age suffer from dysmenorrhoea and in 10 per cent of cases it can interfere with daily life.

Ibuprofen is currently the only non-prescription non-steroidal anti-inflammatory drug that is licensed to treat dysmenorrhoea. Naproxen has been licensed as a prescription-only medicine in the UK for over 30 years; it has been available as a non-prescription medicine in Europe, the US and Australia since the 1990s.

Galpharm International is proposing that naproxen tablets 250mg are made available in a maximum pack size of nine tablets (three

days' supply at a maximum daily dose of 750mg). In terms of its gastrointestinal safety, Galpharm says that ulcer disease is infrequent in women less than 50 years old, and that this, along with limiting the pack size and emphasising that women should titrate to the lowest effective dose, should result in a low risk of gastrointestinal adverse events.

A consultation on the POM to P switch of tranexamic acid for the treatment of heavy menstrual bleeding is currently under way (*PJ*, 10 February, p153). These proposed switches tie in with a wider MHRA initiative of increasing availability of medicines for women's health.

Comments should be sent to Veronica Popo, Room 14-138, Market Towers, 1 Nine



Women with period pain could soon be able to purchase naproxen over the counter

Elms Lane, London SW8 5NQ (e-mail veronica.popo@mhra.gsi.gov.uk) by 23 May. The consultation document is available on the MHRA website at [www.mhra.gov.uk](http://www.mhra.gov.uk) and via *PJ Online* ([www.pjonline.com/links/pj](http://www.pjonline.com/links/pj)).

## Two-phase design for Scotland's chronic medication service

Scotland's chronic medication service (CMS) will be structured in two phases, it was announced this week. CMS is one of the four core services in the new community pharmacy contract.

Bill Scott, chief pharmaceutical officer, Scottish Executive, made the announcement at the community pharmacy practitioner champions' workshop in Edinburgh on 16 April. "A clinical specification for the chronic medication service has been drawn up and is sitting with the Scottish Pharmaceutical General Council for its consideration," he said.

In the first phase of CMS, patients will register with a pharmacy in order to receive advice about how to take their medicines, with the pharmacist solving problems without referring to the prescriber. This might include helping a patient with inhaler technique or addressing side effects by, for

example, advising the patient to take a medicine that causes drowsiness at night.

In phase 2 of CMS, the pharmacist will manage a patient with a long-term condition for up to 12 months. This is where repeat dispensing will fit into the new contract.

Mr Scott believes that CMS will be in place by April 2008. But he pointed out: "The rate-limiting step is for SPGC to respond to the clinical specification. The window of opportunity is open at the moment but it will close, so it is very important these decisions are made now."

In response, Harry McQuillan, SPGC chief executive, said: "I agree this is the rate-limiting step but I think it is worth taking time when making such a fundamental decision. We have got to get it right."

A full report of the meeting will appear in next week's *Journal*.

### News in brief

#### Early PPI use for bleeding ulcers

Early intravenous infusion of a high-dose proton pump inhibitor before endoscopy is justified, having a therapeutic effect on bleeding ulcers, say researchers. They tested the approach using omeprazole as an 80mg bolus followed by an 8mg per hour infusion in a trial of 638 patients. Compared with placebo, omeprazole accelerated resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy (*New England Journal of Medicine* 2007;356:1631).

#### AAH weight management service

An enhanced version of AAH's weight management service has been launched, which incorporates a risk assessment tool and runs over six months. AAH says that it has had a positive response from local pharmaceutical committees and practice-based commissioning clusters to the new service, which it hopes could help pharmacists tap into funding for local care.

#### Irish pharmacy regulation

The Pharmaceutical Society of Ireland, which has a wholly elected council, is to be dissolved and replaced by a new society with a lay majority of 11 on its council of 21 appointed members. The new society has purely regulatory functions (*PJ*, 17 March, p297).

## PCC issues obesity guidance

A framework for managing obesity in primary care has been published by NHS Primary Care Contracting this week. PCC has also published primary care service frameworks for long-term conditions, support for self-care and sexual health.

The frameworks are generic service specifications designed to help commissioners and providers consider an integrated approach to enhanced service provision in primary care. They also describe what contractual routes would be the most appropriate to adopt locally. The frameworks are available at [www.primarycarecontracting.nhs.uk](http://www.primarycarecontracting.nhs.uk).

## Wales sets clock to improve care of chronic conditions

Medicines management for people with chronic conditions needs to improve within three years, the Welsh Assembly Government has said.

As part of a "framework for action" on the management of chronic conditions in Wales, WAG says that developments in pharmacy should be aimed at improving medicines management by April 2010, and at providing evidence for such improvements. Local action plans should be produced by April 2008 and implemented by April 2009, it adds.

# Nottingham researchers win joint Queen's Award



Nottingham university's school of pharmacy and its spin-off company recognised as innovators

The University of Nottingham School of Pharmacy and Molecular Profiles, a spin-off company from the university, have received a joint innovation award in the Queen's Awards for Enterprise.

The Co-operative Group, which includes the Co-operative Pharmacy, is also recognised in the awards. The business received the sustainable development award.

The school of pharmacy and Molecular Profiles — set up as a spin-off in 1997 — are recognised in the continuous innovation and development category for their approach to the analysis of pharmaceuticals using nanotechnology-based methods.

A spokesman for the Queen's Awards office described the school as an internationally recognised centre of excellence in nanotechnology research.

"This research is producing exciting breakthrough results. The school is enhancing significantly the development of new medicines," he added.

Molecular Profiles develops novel applications based around advanced surface analysis and nanotechnologies to provide an insight

into the chemical, physical and material properties of pharmaceutical and biomedical products.

Its services include nanoscreening technology for predicting the ease of development of a new medicine, a deformation service for pin-pointing product problems down to the nanoscale and advanced imaging for viewing and optimising the internal structure of products.

Nikin Patel, Molecular Profiles chief executive officer, said: "Our services and technology are extremely innovative but it is our scientists who develop the rapid response solutions that solve our customers' challenges. This award recognises their expertise and commitment in making Molecular Profiles a cutting edge global contract research company."

Martyn Davies, chairman and a founder of Molecular Profiles and professor of biomedical surface chemistry at the school of pharmacy, added: "Our company was founded on innovation and I am proud to say that ethos has remained as the company has grown successfully over the last 10 years."

## Plans to lift hospital manufacturing standards

Draft good practice guidelines on small-scale manufacturing by hospital pharmacies will demand higher standards than currently apply in many UK hospitals.

The guidance, produced by the international Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), aims to convert standards of industrial good manufacturing practice into something more relevant to smaller units.

A response to the proposals prepared by the Royal Pharmaceutical Society and compiled from comments made by UK hospital pharmacists suggests that compliance with the proposed standards would increase both workload and cost.

Among proposals that would drive up workload are plans to require higher standards of documentation, including assessments of the therapeutic need for any products, along with information on their

safety, toxicity, biopharmaceutical characteristics, stability and design before they can be made. Anything that is to be made repeatedly would also need baseline quality control data and stability information.

Costs would be pushed up by higher standards of protective clothing, more frequent cleaning or replacement of reusable items, such as cleaning mops, and more frequent environmental testing.

When consultation on the draft started in October 2006, Tobias Godschan, head of the PIC/S expert circle on hospital pharmacy, said: "The key element of the new guide is the demand for a comprehensively designed and correctly implemented quality assurance system incorporating the principles of good manufacturing practice."

He said that the proposed requirements were based on risk and adopted a graduated approach based on product types and quantities.

## Senecio ban to be formalised

Having proposed a prohibition on unlicensed herbal medicines containing *Senecio* species early in 2004 (*PJ*, 7 February 2004, p148), the Medicines and Healthcare products Regulatory Agency is now consulting on proposed legislation which will implement the ban.

*Senecio* species contain unsaturated pyrrolizidine alkaloids, which are known to cause potentially fatal veno-occlusive disease. The legal ban will reinforce a voluntary agreement by herbal medicine suppliers not to supply senecio products.

## Brain cancer alliance set up to develop research in NW

The School of Pharmacy and Pharmaceutical Sciences at the University of Central Lancashire is part of a new strategic alliance that will develop research programmes aimed at tackling brain cancers.

The alliance, known as Brain Tumour North West, involves the University of Central Lancashire, the University of Wolverhampton and the Lancashire Teaching Hospital's NHS Foundation Trust.

The alliance hopes to stimulate research by opening access to rare tumour material and sharing laboratory facilities and techniques, as well as pooling scientific, medical and statistical expertise.

One element of Brain Tumour North West's work will be establishing a "brain bank" at the Royal Preston Hospital.

## European guidelines on first-in-man clinical trials proposed

Draft guidelines on first-in-man clinical trials have been published by the European Medicines Agency (EMA).

The guidelines have been developed in response to the severe adverse events suffered by volunteers in the TGN1412 trial at Northwick Park in March 2006 (*PJ*, 18 March 2006, p307).

The EMA aims to provide a common approach across EU member states to the design and conduct of first-in-man clinical tri-

als of high-risk products. The guidelines broadly mirror the suggestions made by the Government's expert scientific group on pre-clinical and phase I trials (*PJ*, 16 December 2006, p727), including recommending sequential dosing and adequate intervals between doses.

Consultation on the guidelines, which are available from the EMA website ([www.emea.eu.int](http://www.emea.eu.int)) and via *PJ Online* ([www.pjonline.com/links/pj](http://www.pjonline.com/links/pj)), will close on 23 May.

## First DPP-4 inhibitor launched

Sitagliptin, the first in a new class of oral anti-hyperglycaemic agents, has been launched by Merck, Sharp & Dohme.

Marketed as Januvia, sitagliptin is the first dipeptidyl peptidase 4 (DPP-4) inhibitor to be made available. It increases levels of incretin hormones, which leads to increased levels of insulin, and reduced levels of glucagon, being released.

Sitagliptin is indicated for the improvement of glycaemic control for patients with type 2 diabetes mellitus, in combination with metformin, when diet, exercise and metformin do not provide adequate glycaemic control or, in combination with a thiazolidinedione, when diet, exercise and a thiazolidinedione do not provide adequate glycaemic control. The summary of product characteristics advises that Januvia should not be used to treat patients with type 1 diabetes or patients with moderate to severe renal in-



Januvia is indicated for the improvement of glycaemic control for patients with type 2 diabetes

sufficiency or for the treatment of diabetic ketoacidosis.

Shailen Rao, an independent consultant pharmacist with experience of diabetes care, told *The Journal*: "Sitagliptin is a useful addition to the range of existing treatments for glucose control in type 2 diabetes. It will provide an alternative to glitazones and especially for patients where hypoglycaemia with sulphonylureas is a problem."

## Ovarian cancer risk is increased for women who use hormone replacement therapy

Women who use hormone replacement therapy are at increased risk of ovarian cancer, data collected from the Million Women Study confirm.

Researchers calculated that for every 1,000 women using HRT, 2.6 developed ovarian cancer over five years, compared with 2.2 per 1,000 in women who did not use HRT. This translates to one extra ovarian can-

cer diagnosed in every 2,500 HRT users, and one extra death from ovarian cancer in every 3,300 users. Risk did not differ significantly by type of HRT preparation used, its constituents, or mode of administration and returned to that found in women who had never used HRT after women stopped using it. The study was published online in *The Lancet* on 19 April ([www.thelancet.com](http://www.thelancet.com)).

## Pharmacists can help fill gaps in care for patients with depression

There are considerable gaps in the care provided for people with depression, which could be addressed by improvements to the GP contract, according to a report published by mental health charities Depression Alliance and SANE to coincide with depression awareness week.

Carol Paton, chief pharmacist at Oxleas NHS Foundation Trust, who provided advice and guidance during development of the report, told *The Journal* that several of the issues identified are also relevant for pharmacists.

"There is a huge amount that pharmacists can do to help patients with depression. The most obvious help that pharmacists can provide is around the management of antidepressant drugs. Pharmacists can make sure that patients who are collecting their first

prescription for antidepressants are aware that there will be a time lag before their symptoms begin to respond and that the outcome from treatment will be improved if medication is continued for six months after symptoms have resolved." She added that pharmacists have a valuable role in signposting patients to local charities and voluntary sector organisations. They could also help by being aware of the association between depression and chronic physical health problems such as cardiovascular disease and diabetes. "Pharmacists should be vigilant to the signs of depression in these patients and encourage them to speak to their GP so that the condition can be diagnosed and treated."

The report "Now we're talking!" details results from a survey of 450 people with de-

## Paediatric depression trials

A new meta-analysis of paediatric trials supports the view that use of antidepressants in children and adolescents for major depressive disorder, obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders increases the risk of suicidal behaviour. However, the researchers argue that the risk is small and should not preclude the careful use of these agents, which they say are effective, particularly for non-OCD anxiety disorders (*JAMA* 2007;297:1683).

## Poor knowledge of diabetes

People who have type 2 diabetes are often poorly informed about the condition, the results of a survey published by the International Diabetes Federation this week suggest.

Across 787 subjects with poorly controlled type 2 diabetes in the UK, France, Germany, Italy and Spain, 40 per cent had never heard the term HbA<sub>1c</sub> or did not know what it meant. Of those who recalled having an HbA<sub>1c</sub> test, 31 per cent did not know what their most recent HbA<sub>1c</sub> level was.

The survey also showed that 68 per cent of respondents would be concerned or very concerned about switching to insulin. Just over three quarters (76 per cent) thought it would restrict their lives and 55 per cent thought that self-administering insulin would be complicated. In addition, 44 per cent believed that if insulin treatment were suggested they would have no choice but to accept it.

In addition, preliminary results of a Healthcare Commission survey of 68,500 people in England with diabetes were published last week. The survey found that many people either were unaware of which type of diabetes they had (17 per cent) or were mistaken about which type they had (5 per cent). Forty per cent said they were rarely or never given the chance to discuss different medicines they could take.

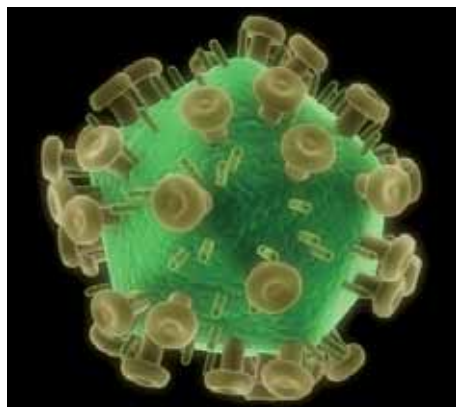
# Phase II data positive for HIV drug

The first in a new class of drugs to treat HIV has shown promise in a phase II trial of patients with few remaining treatment options. Published last week in *The Lancet* (2007; 369:1261), the study demonstrated superior viral control of raltegravir — a HIV-1 integrase inhibitor, formerly MK-0518 — over placebo at three different doses (see Panel).

The primary endpoints of the study were change in patients' viral load after 24 weeks and treatment safety. Compared with placebo, significant reductions in viral load (from baseline at week 24) were seen for patients receiving raltegravir 200mg (difference  $-1.45 \log_{10}$  copies per ml, 95 per cent confidence interval  $-1.84$  to  $-1.06$ ;  $P < 0.0001$ ), raltegravir 400mg ( $-1.52$ , CI  $-1.90$  to  $-1.14$ ;  $P < 0.0001$ ) and raltegravir 600mg ( $-1.49$ , CI  $-1.85$  to  $-1.13$ ;  $P < 0.0001$ ).

The authors say that the safety of raltegravir was similar to that of placebo, and no dose-related toxicities were identified.

They conclude: "The promising efficacy and tolerability profile of raltegravir suggests that this drug has the potential to become an important component of combination treat-



HIV virion, three-dimensional model

ment regimens used to treat heavily pre-treated patients failing current therapies with multidrug-resistant virus and limited treatment options."

[Phase III investigations of the drug are already under way — early data were reported at a recent conference (*PJ*, 17 March, p303).]

Writing about the drug's pharmacology and clearance in an accompanying comment (*ibid*, p1235), Pedro Cahn and Omar Sued from the Department of Clinical Research, Fundación Huésped, Buenos Aires, say: "The integrase inhibitors target an essential enzyme for the HIV-1 virus that catalyses the insertion of HIV-1 DNA into the host's cellular genome. This process is required for expression and high-level HIV-1 replication. Integrase also affects retrotranscription and viral assembly. Host cells lack this enzyme, hence toxicity at this level is not expected."

They go on: "The major mechanism of clearance of raltegravir in human beings is UGT1A1-mediated glucuronidation. Raltegravir does not inhibit or induce cytochrome P450 enzymes, nor is it a substrate there, which implies that interactions with ritonavir and other drugs metabolised via this system are unlikely."

## Rapid genotyping assay could simplify warfarin dose choice

Genotypes affecting the dose-response to warfarin can be accurately detected with a rapid genotyping assay that could simplify dosage decisions, according to data reported at the American College of Cardiology 2007 Scientific Sessions held in New Orleans last month.

The trial tested a rapid genotyping method, based on the finding that variability in patient response to warfarin is caused, in part, by variations in the cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes.

Patients' DNA was extracted from buccal swabs and a polymerase chain reaction was used to amplify it for the VKORC1 and CYP2C9\*2 and \*3 polymorphisms. The one-hour test means that results can guide optimal warfarin dosing without delaying initiation of therapy.

## Retigabine reduces frequency of partial-onset seizures

Adjunctive therapy with the novel antiepileptic drug retigabine (see Panel) reduces the frequency of partial-onset seizures for patients, according to a recently published study (*Neurology* 2007;68:1197).

Patients taking retigabine daily in three divided doses saw dose-dependent improvements in monthly seizure frequency (600mg/day, percentage change from baseline  $-23$  per cent; 900mg/day,  $-29$  per cent; 1,200mg/day,  $-35$  per cent; placebo,  $-13$  per cent;  $P < 0.001$  for overall difference across all treatment arms).

The study had a 32 per cent dropout rate, with confusion, speech disorder, dizziness and somnolence the most common side effects that led to discontinuation. Of the patients who left the trial, 91 per cent did so during the "forced titration" phase of the trial which, the authors say, was necessary to separate the treatment arms but disadvantaged patients who might have tolerated a more flexible approach.

### How retigabine works

Retigabine, a carbamic acid derivative, shows broad-spectrum anticonvulsant action through the following mechanisms:

- Enhancing potassium current mediated by human KCNQ2 and KCNQ3 potassium channels
- Potentiating gamma aminobutyric acid (GABA)-evoked currents in cortical neurons
- Blocking 4-aminopyridine-induced neosynthesis of neuroactive amino acids
- Stimulating *de novo* synthesis of GABA in hippocampal slices

### Study subjects

Investigators recruited 179 adult patients with:

- HIV-1 RNA viral load over 5,000 copies per ml
- CD4 cell counts over 50 cells per  $\mu$ l
- Documented resistance to at least one nucleoside reverse transcriptase inhibitor, one non-nucleoside reverse transcriptase inhibitor and one protease inhibitor

All patients were given an optimised background regimen based on individual antiretroviral treatment history and were randomised to receive 200mg, 400mg or 600mg of raltegravir or placebo orally twice a day.

## Tolvaptan improves heart failure symptoms but not mortality

Tolvaptan, given for the acute treatment of patients admitted to hospital for heart failure, can improve patients' symptoms but has no effect on long-term mortality or further hospital admissions, results from two studies published in *JAMA* indicate.

In both studies EVEREST (efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan) investigators followed the same 4,133 patients randomised to receive tolvaptan — a vasopressin V2 receptor blocker (*PJ*, 8 May 2004, p565) — or placebo in addition to standard therapy including diuretics. Patients received tolvaptan within 48 hours of admission and for a minimum of 60 days.

The short-term study (*JAMA* 2007;297:1332) used a primary endpoint that encom-

passed changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge if earlier. The tolvaptan group saw greater improvement than placebo ( $P < 0.001$ ).

The incidence of serious adverse events, notably renal failure and hypotension, was similar between groups.

However, the other study (*ibid*, p1319), which followed up the same patients long term, showed no difference between tolvaptan and placebo in terms of mortality and heart failure-related morbidity.

The authors say that tolvaptan is the first agent evaluated for patients admitted to hospital with worsening heart failure for which short-term symptomatic benefit and long-term safety has been established.