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From the Editor

The National Pharmacovigilance System has reached the 200 ADR reports/million inhabitants/year mark in 2009, thus getting very close to the "ideal" rate of 250-300 ADR reports/million inhabitants/year. Growing awareness on the part of health professionals, namely physicians, pharmacists and nurses, of the importance of actively participating in post-marketing medicines safety surveillance activities most probably account a great deal for this rather positive trend.

Further in this issue, the following are highlighted: increased mortality in the elderly and risk of venous thromboembolism with antipsychotic drugs, the potential occurrence of meningiomata with prolonged ciproterone therapy, and the withdrawal of a topical antiinflammatory agent whose risk of allergic skin reactions seems to outweigh its limited therapeutic benefit.

From the literature come considerations on the venous thromboembolic risk profile of recent oral contraceptive agents, as well as evidence on the safety of giving certain vaccines to hypocoagulated patients, and a reminder on the relevance of weighing in medicines when making the differential diagnosis of the etiology of headaches.

The section on drug interactions adresses key safety points for the pharmacotherapeutic management of hypertensive, angina and dyslipidaemic patients.

How can I report an adverse reaction?

Postage Paid Card

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

Medicines Risk Management Dept. (Pharmacovigilance) at INFARMED I.P.
Ph.: 217 987 140 - Fax: 211117541
E-mail: farmacovigilancia@infarmed.pt

OR

Northern Regional Pharmacovigilance Unit
Tel: 225 513 661 - Fax: 225 513 682
E-mail: ufn@med.up.pt

Centre Regional Pharmacovigilance Unit
Tel: 239 480 100 - Fax: 239 480 117
E-mail: ufc@aibili.pt

Lisbon and Tagus Valley Regional Pharmacovigilance Unit
Tel: 217 802 120 - Fax: 217 802 129
E-mail: uflvt@sapo.pt

Southern Regional Pharmacovigilance Unit
Tel: 217 971 340 - Fax: 217 971 339
E-mail: urfsul@ff.ul.pt

Antipsychotic agents: increased mortality in elderly patients with dementia and risk of venous thromboembolism

Following on an assessment of the available data on increased mortality in elderly patients with dementia and risk of venous thromboembolism (VTE), associated with the use of antipsychotics, the European Pharmacovigilance Working Party (PhVWP) at EMA has reached the conclusion that all the SPCs and Information Leaflets of medicines authorized within the EU which contain the active ingredients listed below should include the following details:

TYPICAL ANTIPSYCHOTICS *: Risk of VTE and increased mortality in elderly people with dementia

SPC Section 4.4 - Special warnings and precautions for use

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with [...] and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are not treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

[...] is not indicated for the treatment of behaviour disorders associated with dementia.

SPC Section 4.8 - Undesirable effects

[Medicines for which no cases have been reported:]

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs - Frequency unknown

[Medicines for which cases have been reported:]

Venous thromboembolism should be listed as appropriate.

OTHER ANTIPSYCHOTICS: Risk of VTE**

SPC Sections 4.4 and 4.8: as above for VTE

Joana Oliveira

** Benperidol, chlorpromazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, perphenazine, pimozide, pipothiazine, prochlorperazine, promazine, sulpiride, trifluoperazine, zuclopenthixol.*

*** Acepromazine, amisulpiride, aripiprazol, bromoperidol, buspirone, chlorprothixene, clotiapine, clozapine, cyamemazine, dixyrazine, loxapine, melperone, olanzapine, paliperidone, penfluridole, pericyazine, pipamerone, prothipendyl, quetiapine, risperidone, sertindole, tiapride, ziprasidone, zotepine.*

Ciproterone: meningiomas

Triggered by a publication in the medical literature (Froelich S, Dali-Youcef N, Boyer P, et al. Does cyproterone acetate promote multiple meningiomas? Endocrine Abstracts. 2008; 16: P158.), the European Pharmacovigilance Working Party reviewed all available evidence on a possible causal relationship between cyproterone acetate (CPA) and the occurrence of meningioma. The review covered data from the medical literature, spontaneous reporting, a pharmacoepidemiological study, dose-responsiveness data as well as mechanistic considerations.

In view of the available evidence, the PhVWP concluded that the administration of ciproterone acetate at **doses of 25mg and more** for a long time period (i.e. **years**) could at least be possibly causally related with the occurrence of (multiple) meningiomas.

Thus an agreement has been reached to update the SPCs and Information Leaflets of medicines containing ciproterone acetate in **formulations higher than 2 mg**:

SPC section 4.3 - Contraindications

[…] must not be used in patients with meningioma or a history of meningioma.

SPC section 4.4 - *Special warnings and precautions for use*

The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25mg/day and above. If a patient treated with [...] is diagnosed with meningioma, treatment with [...] must be stopped (see section 4.3).

SPC section 4.8 – Undesirable effects

The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproteronacetate at doses of 25mg/day and above.

Alexandra Pêgo

INDEX CARD | **Director:** Júlio Carvalhal **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Ana Araújo, Cristina Mousinho, Cristina Rocha, Fátima Bragança, João Ribeiro Silva, Joana Oliveira, Luís Pinheiro, Magda Pedro, Margarida Guimarães, Pedro Marques Silva. **Publishing Assistant:** Inocência Pinto. **Advisory Board:** Vasco Maria, Luísa Carvalho, Hélder Mota Filipe (INFARMED, I.P. Executive Board); INFARMED, I.P. Medicines Evaluation Committee. **Publisher:** INFARMED - National Authority of Medicines and Health Produts, I.P., Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, E-mail: infarmed@infarmed.pt **Design and Prodution:** nsolutions - design e imagem, lda. **Printing:** Peres-Soctip, S.A. **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 40.000

2009: one year of ADR reports

Since the start of the Portuguese National Pharmacovigilance System (NPS) in June 1992 and until December 2009, the annual number of adverse drug reaction (ADR) reports received increased steadily (Fig. 1).

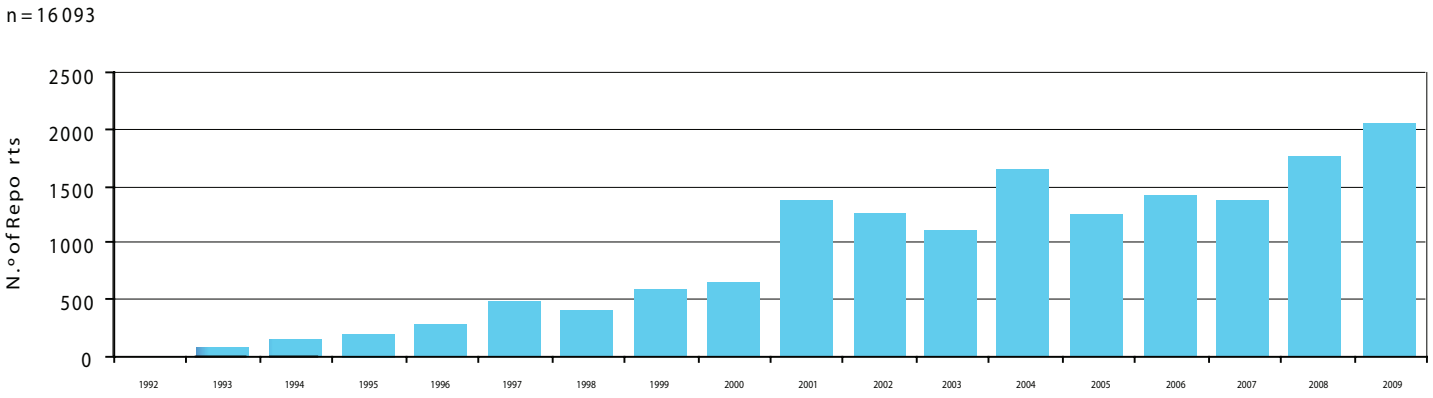

Figure 1. Evolution of the number of ADR reports in the National Pharmacovigilance System

In 2001, the Regional Pharmacovigilance Units (RPU) were installed. They contributed towards a rise in the number of ADR reports received by the NPS. The pandemic influenza A H_1N_1 vaccine, which began to be administered in October last, generated 7% of the total number (2038) of ADR reports in 2009.

Even though the yearly reporting trend seems to be clearly positive, reporting rates in Portugal still fall behind the international **"gold standard"**: **250-300 reports per one million inhabitants per year**. However, trends in recent years and the figures reached in 2009 (**200 reports/million inhabitants**) seem to suggest that the above target may be attained in the relatively short run.

Throughout the NPS's 18 years of existence, a total 16,093 ADR reports have been entered. Most of them meet the **minimum criteria** that are necessary for initial validation, namely: an identified report originator who can be reached by the System, a suspected medicine, an adverse reaction, the patient's demographic data, such as age and gender. Still, there is often the need to obtain further data in order for a given case to be more thouroughly assessed or causality to be ascertained. This prompts the System to contact the reporting professional. Importantly, the NPS ensures that the patient's and the reporting professional's data are kept strictly **confidential**.

NPS data from 2009 are presented, namely concerning the channel used (direct or indirect), the professional groups that make the most reports, and the origin and seriousness of the reports.

The reporting channel that health professionals most used in 2001 and 2009 (Fig. 2) was the **direct** one, by sending in the reports to INFARMED I.P. or to one of the RPUs, either by post or, more recently, online (Northern, Southern, and Central Portugal RPUs). The **indirect** route **through a Marketing Authorization Holder** (MAH) has been progressively increasing, from 205 in 2001 to as many as 915 in 2009.

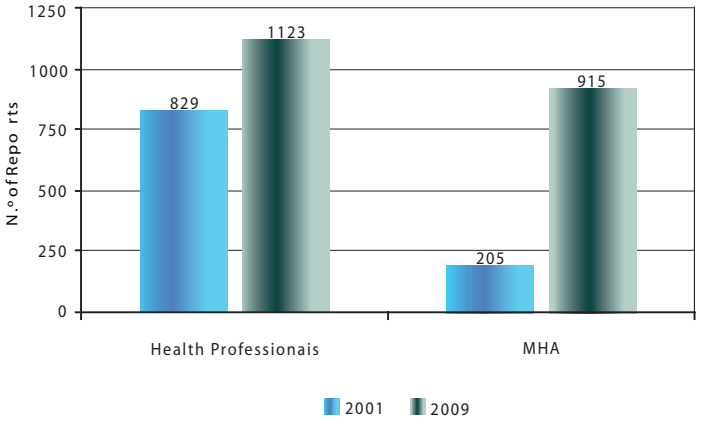

Figure 2. ADR report according to channel used in 2001 and 2009

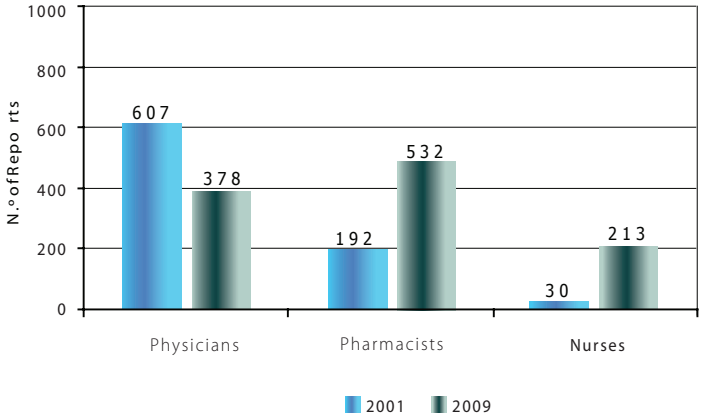

Figure 3. ADR reports according to health professional group in 2001 and 2009

In 2009, 55% of all reports were entered through the direct route, while the remainder reached INFARMED I.P. through MAHs to whom health professionals had reported cases from their daily practice. MAHs sent in most reports electronically (XML files), and only 4% were entered in paper form.

With time, **several health professional groups have progressively become involved** in the System. Physicians have been taking part since the NPS started in 1992. Pharmacists began to report in 1995; however, until 1998, their ADR reports were only entered in the System provided the patient's doctor had validated them. This requirement ceased in 1998. Nurses, on the other hand, have been participating in the NPS since the year 2000, and they are actually the originators of most ADR reports concerning vaccines.

From 2001 to 2009 (Fig. 3) the number of ADR reports increased steadily, both those originated by pharmacists and by nurses. This has been matched by a decrease in the number of physician originated reports, possibly because they have been choosing to use the indirect route via MAHs. In 2009 **pharmacists were the number one ADR report originators** with close to half (47%) of all reports sent in by health professionals via the direct channels, followed by physicians and nurses. This may be to do with a higher number of training sessions that have been offered to pharmacists in general.

In geographical terms (Fig. 4), the most reports in 2009 came from the **Lisbon and Tagus Valley** region (37%), followed by the Northern region (29%), Southern (16%), and Central Portugal (15%). The Azores and Madeira islands accounted for 3% of the total of ADR reports nation-wide.

What do they stand for?!

ADR Adverse Drug Reaction

CHMP Committee for Medicinal Products for Human Use

EMA European Medicines Agency

PIL Patient Information Leaflet

MA Marketing Authorisation

SPC Summary of the Product's Characteristics

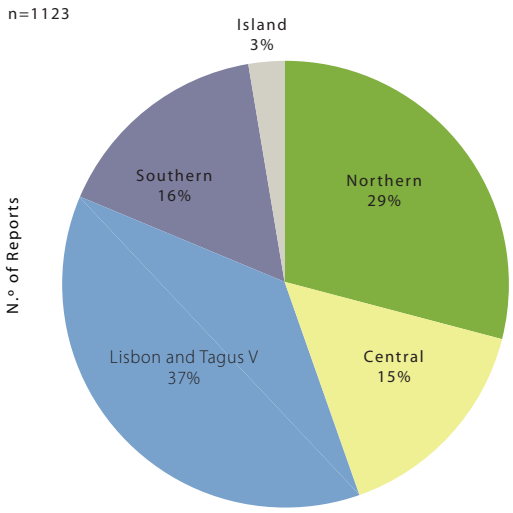

Figure 4. Geographical distribution of ADR reports in 2009

Out of all cases received by the NPS, circa **73%** (1497) were **serious**. Of these, 61% were sent in by MAHs, 17% by physicians and another 17% by pharmacists, the remainig cases having been reported by nurses, especially serious vaccine reactions (Fig. 5). It should be noted that MAHs, within the scope of the spontaneous reporting system and according to current legislation, only communicate serious cases expeditously (within 15 days), whereas non-serious cases are at a later date included in the periodic safety update reports they send to INFARMED I.P. on scheduled dates.

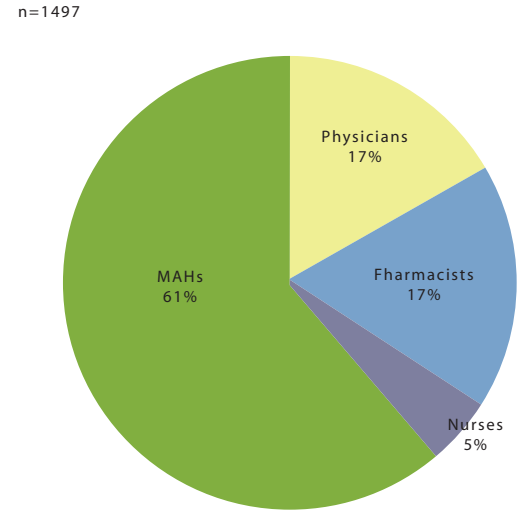

Figure 5. Distribution of serious cases reported according to originator group in 2009

The safety profile of any given medicine is a dynamic factor that changes constantly along with clinical practice. Spontaneous reporting of ADRs is a method that promotes the surveillance of medicines after they have been introduced in the marketplace. One of the main oucomes of spontaneous ADR reporting activities is early detection of possible safety problems (**signals**) which may arise from the use of medicines and which may until then have been going totally unnoticed.

Computerised signal detection methods are well under development, but the health professionals' endeavour will probably always be of the utmost relevance for case detection. ADR reports are indeed indispensable if we are to better now the safety profile of medicines and to give a major contribution to public health protection.

Do send us your suggestions and report any ADRs you supect. This is what makes the National Pharmacovigilance work.

Fátima Pereira de Bragança

Bufexamac (Parfenac®): withdrawn

INFARMED I.P. has withdrawn from the market Parfenac® ointment (50 mg/g), based on a safety and effectiveness data review carried out by the CHMP at EMA, which concluded that bufexamac's benefits are not such as to clearly outweigh its risks.

Bufexamac is a topical non-steroidal antiinflammatory agent which has been in the European market since the 1970s. It has very limited effectiveness data, and was indicated for the treatment of various skin disorders, including eczema, burns, erythematous rash, etc. A high risk of contact allergic skin reactions has been identified. These reactions can sometimes be serious, especially in patients with predisposing conditions, such as certain forms of eczema for whose treatment bufexamac was indicated. Furthermore, the allergic reactions caused by this drug can be very similar to the underlying disease, which may cause a correct diagnosis and therapy to be delayed.

Alexandra Pêgo

ADRs in the Literature...

Ethinylestradiol + Drospirenone: risk of venous thromboembolism

Recent studies suggest that the risk of venous thromboembolism for the Yasmin®/ Yira® contraceptives is between that of second and third generation pills.

Venous thromboembolism (VTE) is a well-known but rare adverse reaction of oestrogen- and progestogen-containing contraceptives. Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use combined oral contraceptives (COCs) with a low dose (<50 µg) of ethinylestradiol (EE) combined with levonorgestrel ("second generation pills") is about 20 cases per 100,000 woman-years of COC use, and about 40 cases per 100,000 women-years of COC use for products containing low-dose EE and desogestrel/gestodene ("third generation pills"). In women who do not take any hormonal contraception, 5 to 10 VTE cases occur per 100,000 woman-years.

Recently, two epidemiological studies were published*,** both assessing the risk of VTE in current users of different types of COCs. The results of these studies confirmed what is currently known about this risk, but also suggested that the risk for the COCs Yasmin® and Yira® might be higher than previously estimated, and between those of second and third generation pills. Yasmin® and Yira® contain 30µg of EE in combination with drospirenone.

The two studies were discussed by the PhVWP, and it was concluded that the new data should be reflected in the Summaries of SPCs for Yasmin® and Yira®. The amendment of the SPCs will be processed via variations of the marketing authorisations within the mutual recognition procedure.

Margarida Guimarães

** Lidegaard Ø et al. Hormonal contraception and risk of venous thromboembolism: a national follow-up study. Br Med J. 2009; 339: b2890.*

*** Van Hylckama Vlieg A et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestagen type: results of the MEGA case-control study. Br Med J. 2009; 339: b2921.*

ADRs in the Literature...

Patients on warfarin can be safely immunized against seasonal influenza, pneumococcal infections, tetanus, and hepatitis A

In a retrospective cohort study on 5167 members of a US health maintenance organization who were on hypocoagulation therapy with warfarin, immunization with vaccines for seasonal influenza, pneumococcal infection, tetanus and hepatitis A, did not significantly change their INR levels, until as late as 28 days after vaccination.

Jackson ML, et al.; for the Vaccine Safety Datalink investigators. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. Pharmacoepidemiol Drug Saf. 2007 Jul;16(7):790-6.

Erratum

1st Term 2010 issue
Article on Propylthiouracil: risk of serious liver impairment.
The first introdutory line should read:
Propylthiouracil has been used for the treatment of hyperthyroidism for over 50 years.

ADRs in the Literature...

Headache: are you on any medication?

Headaches as adverse reactions are frequent and do not always get attention that will match the functional and quality of life compromise they often cause. On the other hand, given the elevated baseline prevalence of headaches in the general population, ascribing causality of this type of symptoms to a medication is not always straightforward.

Headaches characteristic of drugs or classes of drugs

Type of headache	*Drug*
Migraine without aura	Cyclosporin, Dipyridamole, Nitric oxide donors, Phosphodiesterase inhibitors, Interferon-b, Ondansetron, Tacrolimus, Sertraline
Migraine with aura	Nitric oxide donors, Phosphodiesterase inhibitors, Tacrolimus, Fluoxetine
Typical aura without headache	Tadalafil
Cluster headache	Nitric oxide donors, Phosphodiesterase inhibitors

Classification of Headaches according to ADR type

Type of headache	*Defining characteristic*	*Drugs*
Headache as type A adverse reaction	Predictable, related to the principal pharmacological action of the drugs, and dose-dependent	Nitric oxide donors, Phosphodiesterase inhibitors, Calcitonin gene-related peptide-CGRP, Cocaine, Ethanol, Cannabis , Histamine, Calcium-channel blockers, Antiarrhytmics, Beta-adrenergic blockers, ACE inhibitors, Sympathomimetics, Angiotensin II receptor antagonists, Statins, Clonidine, Alpha-Adrenergic blockers, Amiloride, Methylxanthines, Beta-adrenergic agonists, Agents for erectile dysfunction, Ergotamine, Nicotine, Amphetamine
Headache as type B adverse reaction	Idiosyncratic, unpredictable, usually very low incidence (<1/1000)	Amoxicillin, Carbamazepine, Diclofenac, Famotidine, Ibuprofen, Immuneglobulin, Infliximab, Ketorolac, Leflunomide, Levamisole, Metronidazole, Naproxen, Ranitidine, Rofecoxib, Sulfamethoxazole, Sulfasalazine, Sulindac, Tolmetin,Trimethoprim, Valacyclovir
Headache as type C adverse reaction	After chronic medication, or related to raised intracranial pressure	Amiodarone, Anabolic steroids, Contraceptives Combination, Ciprofloxacin, Danazol, Corticosteroids, Gentamicin, Lithium, Nalidixic Acid, Nitrofurantoin, Ofloxacin, Retinoic Acid, Tetracycline, Thyroid hormone replacement, Vitamin A
Headache as type E adverse reaction	Related to substance withdrawal	Caffeine, Opioids, Estrogens, Ergotamine, Cocaine, Methysergide

Ferrari A et al. Focus on headache as an adverse reaction to drugs. J Headache Pain. 2009 Aug;10(4):235-9.

Interactions to keep in mind!

Hypertensive patients*

Risk of:

Worsening hypertension / poor blood pressure control
- Medicines inducing salt and water retention; e.g., corticosteroids.
- Non-steroidal antiinflammatory agents. Risk of renal impairment, especially when associated with a diuretic, an ACE inhibitor, or a sartan.

Renal impairment
- Associations of diuretic / ACE inhibitor / sartan.

Hiperkalaemia
- Association of a potassium-sparing diuretic with an ACE inhibitor or a sartan.

Serious bradycardia
- Association of a beta-blocker with diltiazem or with verapamil. Also adverse effects on conduction and inotropism.

**Based on: la revue Prescrire*

Patients with angina*

Risk of:

Serious bradycardia
- Association of diltiazem or verapamil with a beta-blocker.

Heart failure
- Association of diltiazem or verapamil with a beta-blocker.

Severe hypotension, syncope, ischaemia
- Association of a phosphodiesterase inhibitor (sildenafil, taladafil, vardenafil) with nitrates.

**Based on: la revue Prescrire*

Patients with dyslipidaemia*

Risk of:

Rhabdomyolysis
- Association of a statin with ezetimibe and especially with fibrates.
- Association of a statin with fusidic acid.

Gallbladder lithiasis
- Association of ezetimib with fibrates.

Decreased absorption of various drugs
- Cholestyramine affects the absorption of medicines such as antiepileptic drugs, anticoagulants, oral contraceptives, antibiotics, statins, digitalics, thiazides, levothyroxine, etc. These drugs should be taken 1 hour before or 4 to 6 hours after cholestyramine.

NB 1
The cytochrome P450 system is virtually not involved in the metabolism of **pravastatin** (contrarily to other statins). Therefore, it may be associated with fewer adverse effects in cases where hypolipaemic therapy needs to be given to a patient being treated with enzyme inducers or inhibitors (e.g., epileptic patients, HIV-infected patients).

NB 2
In order to achieve optimal therapeutic intervals, the posology of **antocoagulants** (anti-vitamin K agents) and **cyclosporin** should be adjusted whenever most hypolipaemic drugs need to be either added to or withdrawn from the therapeutic regime.

**Based on: la revue Prescrire*