TABU

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Lääketietoa Lääkelaitokselta

Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Försskåhl

In English | Translation Mervi Moisander

Jussi Holmalahti
Professor, Head of the Enforcement and Inspection Department
National Agency for Medicines

Editorial

What creates a demand for unlicensed or adulterated medicines?

There are thousands of unlicensed operators trading in medicines over the Internet, and it is impossible to estimate the damage they have caused among patients. The medicinal products available on e-commerce are often stolen or fake products with contents not always corresponding to what is promised.

According to an estimate by the World Health Organisation (WHO), about ten percent of all medicines sold on the world market are counterfeit drug. It has been clearly demonstrated that illegal trade of medicines is a branch of international criminal activity in which the operators are identical with those dealing in narcotics and similar doping substances. In the opinion of these operators, the economical and legal risks associated with unlicensed trading in medicines are minimal in comparison with narcotics and doping agents. It would appear that we Finns have lulled ourselves into false security with an illusion of safe e-commerce in medicines.

In news reporting and media discussions the terms legal and illegal medicinal products are concepts which are becoming ever more relative. In the course of such discussions, less guardianship and more freedom are demanded; abandonment of the imposed prescription status of medicines and allowing their retail grocery shop and on-line sale. It amounts to dreaming in public of how a customer could by one opening of a door satisfy an increasing number of needs. There is needs for a market place which is always open, where in addition to alcohol, beer and health food products also “simple over-the-counter and self-medication products” would be on offer as well. Simple medicines, however, have a place only in the imaginary world.

The efficacy, safety and quality of a medicinal product are not based on the special blue colour or the angular shape of a tablet. Even the most common medicinal product is made up of numerous significant, standard and specifically designed properties. Chemically, physically and biologically, a medicinal product is a very complicated invention. Everything about illegal medicinal products is guesswork: no information is readily available about their composition, manufacturing methods. Impurities generated, diluents used, toxic catalysts or potentially carcinogenic constituents will be tested by the users. Bodies responsible for providing this information never make an appearance.

One explanation for the change in attitudes towards medicines is a general interest in the differences in price of medicinal products, i.e. increased consumer cost-awareness. As a top European country in Internet use, Finland is an attractive target for criminals because of the ever increasing number of Finns having an Internet connection at their disposal. Increasing numbers of Finns use this for making alterations to their tax returns or are involved in e-commerce, the on-line buying of a variety of products and services. All of this goes towards increasing consumers’ confidence in the range of services and quality on offer in e-commerce.

The belittling attitudes associated with medicinal product properties are difficult to understand. The risk associated with illegal trade in medicines is borne by the purchaser of the medicine alone. It is a heavy responsibility as one’s own life or that of the nearest and dearest may be at stake.

We all share the concern for illegal trading in medicines, fake medicines and measures to fight against them. The problem is not solved by closing Internet sites, because the problem lies in human beings themselves and in the blind trust in the faceless information on offer on the Internet. To raise the awareness of the members of the public and make them realise the risks involved with illegal trade of medicines and counterfeit drugs is an important effort to educate the public in a situation where the services and products on offer cannot be abolished.

Markku Kaste
Professor
Department of Neurology
Helsinki University Central Hospital

Stroke thrombolysis and the chain of recovery

Stroke is the second most common cause of death following coronary heart disease (1) and it causes a greater loss of quality adjusted life years than any other disease (2). The incidence and mortality caused by stroke are decreasing 2–3% per year in Finland (3), but as our population is ageing, the number of strokes and consequently the need for treatment will double within the next few decades unless we are more successful in the prevention and treatment of stroke (4). Treatment in a stroke unit decreases the stroke patients' mortality and need for chronic institutional care, but the aim is to improve the treatment results further. This applies especially to patients with ischemic stroke since it is the most common stroke, making up about 75–80% of the total (3, 5-7). A significant breakthrough was made in the treatment of acute ischemic stroke patients with the development of thrombolysis, in which also Finland took part (8-11). Participation in the clinical trials of thrombolysis ensured that the treatment is today carried out safely and effectively at our university and central hospitals.

Thrombolysis is appropriate in the treatment of acute ischemic stroke when it can be initiated within 3 hours of the onset of symptoms, the physician who provides the treatment is familiar with the acute treatment of neurological patients, the patients are aged between 18 and 80 years, and there are no contraindications for the treatment. When approving thrombolysis for the treatment of patients with acute ischemic stroke the EU health authorities required that information of all patients who received thrombolysis with approved indications should be included in an official thrombolysis register (SITS-MOST) so that the authorities could monitor the safety and efficacy of the treatment. According to this register, the number of stroke patients receiving thrombolysis in Finland per one million inhabitants is greater than in any other EU country (12). The advantage for Finland is emphasised even more if the frequency of the treatment is compared in the related sister SITS-ISTR register. This register also includes information of patients over 80 and under 18 years of age who have received thrombolysis and those who have received it more than 3 hours after the onset of symptoms, as the efficacy of the treatment will not stop at 3 hours provided that the patients are correctly selected (11, 13, 14).

According to both the SITS-MOST and the SITS-ISTR registers, the neurological emergency room of Meilahti Hospital provides a higher number of thrombolyses than the two next best units combined. Tampere ranks as the third most effective unit in the registers. Even though it is not a question of European championships, this is a signal of the efficacy of the acute stroke care in Finland, since, in comparison with the densely populated countries on the European continent Finland is scarcely populated, our towns are small, and the distance to a hospital providing thrombolysis is often long.

According to the SITS-MOST register, the number of patients receiving early thrombolysis in Finland is the same as in countries such as France, Spain or Italy, where the population is 10-fold greater than in Finland. The efficacy of thrombolysis is in direct relation to time: the sooner the patients are treated the better are the results. In Helsinki, when thrombolysis is given within 60 minutes of the onset of symptoms, 90% of patients recover well. In case the treatment is initiated 90 minutes after the onset of symptoms, 70% of patients recover well (15). Of these early treatments in Finland (within 60, 70, 80 and 90 minutes of the onset of symptoms), about 80% are administered at the neurological emergency room at Meilahti Hospital. This can not be explained only by the fact that the region of Helsinki is the most densely populated area in Finland, but first and foremost by the chain of recovery in which a

lot of planning and training have been invested and which therefore works well. An ancient truism applies here: the chain is no stronger than its weakest link.

The efficacy of thrombolysis is probably best seen in the results of basilar artery occlusion, which is the most devastating stroke. Without thrombolysis, 80–90% of such patients die, and those remaining alive are often in lock-in-syndrome which means that the only active movement the patient is capable of is vertical eye movement (16). With the help of thrombolysis, mortality is reduced by 40% and 25–30% of the patients recover well (17). The fact that thrombolysis is appropriate as part of routine treatment given to patients with acute ischemic stroke and is also effective and safe outside clinical randomised trials, is clearly seen in the results of the recently published SITS-MOST register (18). Only 1,7% of those who had received thrombolysis developed symptomatic intracerebral haemorrhage, and the mortality in those who had received thrombolysis was lower than in those recorded in randomised trials, which initially resulted in the approval of the treatment. The proportion of those who had recovered well was 54,8%, which was slightly higher than that recorded in randomised trials. At this stage the SITS-MOST register contained nearly 6,500 patients from almost 300 hospitals in the European Union, Norway and Iceland, which makes it the largest data ever published about thrombolysis. The register clearly reveals that thrombolysis can be carried out safely and effectively as part of routine clinical practice.

Procedure

In order for the treatment to be safe, the physician providing it should be familiar with the therapeutic indications and contraindications (Table 1, next page) and should know how to interpret the computerised cerebral tomography (CT) of the patient taken in the emergency room (Table 2), because most hospitals do not have a neuroradiologist continuously available. A significant number of Finnish hospitals providing thrombolysis took part in the ECASS and ECASS-II studies (8, 10). In addition, the Finnish Neurological Society has twice arranged training on thrombolysis in which a German Professor, Rüdiger von Kummer, who was a central figure in the development of the criteria by which patient selection is made for thrombolysis, has given lectures on the interpretation of CT. In association with these training sessions he arranged a test for voluntary participants. The first test attracted over 70 neurologists and radiologists of which more than 80% achieved good or excellent marks, a result which Professor von Kummer had not previously seen. The good results probably has contributed to the fact that thrombolysis has become more generally used in Finland than in other European Union countries.

However, good treatment is not enough without a functional chain of recovery. In each hospital district providing thrombolysis the organisation of the chain of recovery has required quite a lot of motivation, energy, education and training, i.e. hard work from all those involved in the chain. Based on the SITS-MOST and SITS-ISTR registers it would appear that this co-operation is better managed by Finnish professionals than by any other Union professionals, which makes you wonder if it is due to the Finnish team spirit.

The significance of the chain of recovery is recognised also in the USA, where thrombolysis was approved for the first time in the world as a treatment for acute ischemic stroke. A task force of the National Institute of Health created a model for the various parts of the chain of recovery, and this gained approval at a wide consensus meeting involving alI parties (19). The model is largely similar to the one used in Finland. In the American model an agreement has been made regionally about which hospital would provide thrombolysis, after which everybody involved, including the emergency centres and paramedics, are trained, and the hospital at which the treatment would be given is allocated the resources to apply it. It would be desirable to have the last-mentioned feature applied in Finland, too, as the use of thrombolysis has not brought additional resources to those hospitals where it is available, despite the fact that the treatment requires heavy

Table 2. *Once the CT is performed, the following points should be addressed when a decision about thrombolysis is to be made for stroke patients.*

CT findings indicative of a recent media infarct (within the past 2–6 hours):

- *insular cortex not visible*
- *the outer edge of the nucleus lentiformis is not visible*
- *capsula interna not visible*
- *difference of sides of the sulci (obliteration)*
- *the density of white matter decreased*
- *the borderline between white and grey matter is not visible*
- *thrombosis in the main trunk of median cerebral artery (hyperdense MCA sign)*
- *mass effect (midline shift seen for more than 6 hours)*

Preconditions for thrombolysis:

- *normal CT or an infarct developing in less than one third of the territory the MCA*
- *no haemorrhage found*

Table 1. Indications and contraindications for thrombolysis in stroke patients		
The answer to all questions must be YES	YES	NO
Previously independent patient (modified Rankin Scale, mRS 0 - 2)		
30 min - 3 hours from the onset of symptoms (basilar thrombosis, up to 48 hours)		
A cerebral infarct at the hemispheric level or suspected basilar thrombosis		
The patient / near relatives have if possible been informed about the treatment		
The answers to all questions must be NO	YES	NO
Initially a seizure with a loss of consciousness and a strong suspicion of Todd's palsy		
Suspected subarachnoid haemorrhage (SAH)		
A history of spontaneous cerebral haemorrhage (excluding SAH if a bleeding aneurysm is closed)		
Cerebral infarct within the past 3 months		
A history of stroke and diabetes (relative contraindication)		
Untreated aneurysm or arteriovenous malformation (relative contraindication)		
Known tendency to haemorrhage		
A severe haemorrhage, trauma or extensive surgery during the past 3 months		
During the past 10 days: external cardiac massage or a puncture of a major vein, which cannot be compressed with a tightening bandage (e.g. v. subclavia or v. jugularis)		
HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelet count)		
Pregnancy or a recent delivery (relative contraindication)		
Malignant or advanced and extensive cancer		
A strong suspicion of endocarditis, septic embolism or pericarditis		
Other severe disease or short life expectancy		
Intracranial haemorrhage seen on cerebral CT imaging		
Is an extensive hypodens area (more than a third of the central cerebral artery vascular area) already to be seen?		
Severe cerebral micro-angiopathy		
Blood pressure 185/110 mmHg or higher despite treatment		
Blood glucose below 2.8 mmol/l or over 22 mmol/l B-gluc		
INR over 1.5 or APTT over 60 s or B-thrombocytes < 100		
Fast recovery from symptoms		
NIHSS 0 - 2		
NIHSS > 25/fixed eye deviation + total hemiplegia + reduced level of consciousness		

on-call duties and fast action, and despite the saving of resources society makes with improved patient recovery (20).

The chain of recovery begins at the emergency centre, when the patient, next of kin or anybody present at the event calls 112. In order for the chain to get started efficiently, the person in the emergency centre should be able to identify a possible acute stroke patient and send the nearest ambulance to the patient. The identification is made easier by memorising the word FAST, which is an abbreviation made up of the words *Face*, *Arm*, *Speech* and *Time*. Paramedics and ambulance personnel are trained to identify patients potentially appropriate for thrombolysis by making a short neurological status in accordance with FAST by asking the patient to grin, answer some questions and squeeze with both hands. If the patient is unable to perform these functions normally and less than 3 hours have passed since the start of the symptoms, an ambulance will bring the patient as an emergency case to the nearest hospital providing thrombolysis. When an ambulance embarks on its transport journey in Helsinki and its environments, the ambulance staff will phone the emergency room at Meilahti Hospital for the first time and give an advance notice of the arrival of a potential patient for thrombolysis. When they are about a 10 minutes' drive away from the emergency room they will call the second time. These advance warnings make it possible for a laboratory technician to meet the patient immediately after his/her arrival and to take necessary blood tests, for the CT equipment to be made available, and for the neurologist to meet and examine the patient already during the transfer to the CT. The speed at which this all happens is also significantly increased by the fact that the CT equipment has been transferred to the premises of the emergency room only about twenty meters distant from the Meilahti Hospital emergency room door and that the thrombolysis is administered while the patient is still lying on the CT table immediately once intracerebral haemorrhage and other contraindications for the treatment have been excluded. With this procedure, *door-to-needle time*, i.e. the time from the ambulance staff opening the emergency room door to the point where thrombolysis is initiated, has been cut from the previous 1.5 hours to less than 25 minutes (12, 21). Reducing the time by an hour is decisive for the level of patient recovery. The motivation prevailing in all the members of the chain is reflected, for example, by the presence of the paramedics at the monitor of the CT of the patient they have brought in, if their emergency duties allow it.

3-hour time window

Not nearly all stroke patients can make it to a hospital providing thrombolysis within three hours of the onset of their symptoms, which is when the official time window closes. Many patients would nevertheless benefit from the treatment even after that (11). These are patients, who after three hours have cerebral tissue, which is suffering from the shortage of oxygen but have not yet infarcted and is thus available for rescue if the occluded artery can be opened early enough. These patients could be identified by modern magnetic resonance imaging (MRI). According to recent studies, it was possible to open about 70% of the occluded cerebral arteries in these patients by using desmoteplase, and of those in whom it was possible to open the blocked cerebral artery about 60% recovered well with thrombolysis which was initiated within up to nine hours of the onset of symptoms (13, 14). Finland took part in the study carried out in Europe (13). The MRI equipment used in these studies is available in all university hospitals and most central hospitals in Finland.

A large international multicenter study, ECASS-III, is ongoing in which an attempt is being made to extend the time window to 4.5 hours. The study was launched by a requirement of the European Union health authorities. The study will be concluded this year and then it will become clear whether the time window can be extended to 4.5 hours. Since Finland takes part also in this study, the results, once ready, will be very appropriate for implementation in the treatment of Finnish ischemic stroke patients. The selection of patients in the ECASS-III study is made by using CT equipment which can be found in all major hospitals with an emergency room.

Stroke Unit

After thrombolysis the patient's follow-up treatment is executed in a stroke unit. According to the Finnish recommendations, the need for rehabilitation of all stroke patients is assessed, the reason and risk factors for stroke are diagnosed, and the treatment of risk factors including secondary prevention and early rehabilitation, is initiated in a stroke unit, and any necessary follow-up rehabilitation is arranged either at a rehabilitation hospital or in an out-patient clinic (22).

Irrespective of whether it is possible to provide thrombolysis and whether it is successful, treatment in a stroke unit is strongly recommended, because it reduces both mortality and the risk for chronic institutional care as well as improves the patient's chance for a good recovery (23, 24). Stroke unit care will maximise not only the results achieved with thrombolysis, but also the secondary prevention and rehabilitation of those pa-

tients who were not eligible for thrombolysis or who did not get it for other reasons. Treatment results achieved in a stroke unit last for at least 10 years (25).

Other recanalisation therapies

Thrombolysis is usually carried out with intravenous alte-plase. If this does not open the artery, the treatment can be continued with intra-arterial thrombolysis. It may sometimes be justified to start intra-arterial thrombolysis straight away (26, 27). This is especially true in stroke patients with extensive clots, such as in a case where the entire carotid artery and middle cerebral artery are occluded, or the entire basilar artery is occluded. Such huge clots do not often open up with intravenous thrombolysis. Efforts have been made to improve recanalisation with extracranial ultrasound (28) and ongoing studies intend to improve the efficacy by in addition to extracranial ultrasound giving the patient intravenous microbubbles (29).

As with coronary heart disease, mechanical recanalisation therapies have also been developed for the treatment of ischemic stroke. These involve a catheter which is inserted in the artery and by which efforts are made to remove the clot the same way as a cork from a bottle of wine is removed (30). The U.S. Food and Drug Administration (FDA) has already approved this type of equipment for clinical use. As a result, the mechanical removal of a clot by using such equipments is rapidly increasing in the USA, but additional proof on whether it improves the outcome of patients is required. For assessing the results, efficacy and safety of the therapy a register known as the MERCI register has been set up in the USA in which all patients given this therapy are entered. Experience of this therapy has already been gained in Finland and Sweden as well, and the two countries are about to join the register.

Telestroke

When the availability of thrombolysis, which is the only effective medical treatment for acute ischemic stroke, is used to evaluate the quality of treatment of stroke at the population level, Finland is the most efficient country in the European Union. The high level of stroke treatment in Finland was also shown in a survey carried out by means of a questionnaire which was sent to randomly selected hospitals in the EU member states. A total of 886 hospitals completed and returned the questionnaire. The survey showed that the treatment of stroke patients was best organised in Finland, Sweden, the Netherlands and Luxembourg (31). But even so, there is great inequality in the availability of thrombolysis also in Finland. In the smaller central hospitals and the still smaller rural hospitals, except at Kuusankoski Hospital, the treatment is not available even during office hours. This inequality could be greatly reduced by the means of telemedicine. At present X-rays, CT imaging and MRI results are transferred electronically in real time from one hospital to another, and video images and sound can also be transferred in real time. By using these communications a patient and a doctor at a smaller hospital and a doctor at a larger university hospital can be in direct visual and speech contact with each other and at the same time examine the results of laboratory tests, CT and MRI performed at the smaller hospital. The neurologist at the university hospital experienced in thrombolysis and in the treatment of stroke patients can help the colleague in the smaller hospital in the choice and carrying out of the treatment, thereby making thrombolysis possible even in the smaller hospital. A fair amount of experience has already been gained about the use of telestroke (32-36).

When projects for the national health programme were selected a few years ago, Helsinki and Uusimaa hospital district proposed telestroke as a nationwide project, but it did not reach the level of a financed project. The telestroke project, in which Helsinki University Central Hospital supports smaller hospitals in their decisions on thrombolysis, was nevertheless launched when the State Provincial Office of South Finland decided to collaborate in the project by undertaking to pay half of the funding required, the other half of which was provided by the hospital districts of Helsinki and Uusimaa, Etelä-Karjala and Kymenlaakso. Time is of the essence in thrombolytic treatment, and therefore it is significantly wiser to transfer know-how than the patient from one hospital district to another. With the help of telestroke and the old Finnish team spirit, support has also been given to the central hospitals of Lapland and Länsi-Pohja. According to the basic principles of Finnish society it is important that all Finns have equal opportunity for thrombolysis. This challenge would be promoted by having the telestroke system cover all hospital districts in the country. When the treat-

ment increases the patient's possibilities to return to normal life in good condition, it is the only humanly correct alternative. Operating telestroke is also economically a sound choice because it generates significant savings for society (20). The same conclusion has apparently been drawn in the USA, as the American Heart Association has set up a task force to write a national recommendation for telestroke. Finland is taking part in this task force.

Communication

Even the most effective acute treatment is of no benefit if patients do not seek for help in time. In myocardial infarction severe pain makes the patient look for help immediately. At the population level there is also evidently high awareness of the seriousness of coronary heart disease and of the fact that treatment is available. Even though good treatment for acute ischemic stroke is now available, the knowledge of it is not widely spread among the population. It is still a very common belief that when a stroke occurs there is nothing to be done, so why rush – especially when the condition is generally not painful. Usually the numbness and weakness of a hand is just being "watched" and treatment is not sought early enough. Few people know that thrombolysis in ischemic stroke is more effective than it is in coronary heart disease, and the difference to the advantage of thrombolysis in stroke grows in line with the speed at which it is administered (37). This is not well-known even among physicians, which may partly explain why the treatment has not been set up quickly in every hospital district in Finland despite the clear instructions given in the recently published Current Care Recommendation about how the treatment should be carried out (22).

Conclusion

Thrombolysis is here to stay. It is aimed at the fast opening of the occluded cerebral artery and thereby at the prevention or at least alleviation of a brain infarction, which would otherwise develop. Further studies will help to prolong the time within which the treatment can be administered, and new, more effective drugs will be developed for recanalisation of occluded brain arteries, including invasive treatments of the type of balloon angioplasty of coronary thrombosis. Developments in the imaging techniques will improve the selection of patients who would benefit from the treatment. Passively waiting for this development to happen is not acceptable; treatment for the population should be arranged NOW (12, 38).

Thrombolysis is the best available treatment, even though it is not appropriate for all patients with acute stroke. All patients would nevertheless benefit from a fast transportation to a hospital with a stroke unit and where thrombolysis is available. Even though thrombolysis in Finland is given to more patients per one million inhabitants than in any other country in the European Union, we are not in an equal position to have thrombolysis when needed. This could be immediately improved by arranging a chain of recovery for acute stroke patients and by facilitating decision-making in smaller hospitals with the aid of telemedicine. The knowledge about acute stroke among the population and about the fact that it is possible to recover from it should also be increased, as well as of the fact that the possibilities of recovery are crucially improved by fast administration of thrombolysis.

See literature on pages 9-10.

Annikka Kalliokoski
Senior Medical Officer
National Agency for Medicines

Leena Sommarberg
Reseacher
National Agency for Medicines

Marja Forsell
Pharmacovigilance Co-ordinator
National Agency for Medicines

Adverse drug reactions in the elderly

The elderly exhibit the same adverse reactions as younger adults do, but owing to changes in the pharmacokinetics of drugs, for example, the elderly may be more sensitive to reactions. Recognising the adverse reactions may be difficult, because they may be considered to be symptoms associated with old age or a disease. Multitherapy, which is usual in the elderly, may make it difficult to recognise the association between the drug used and the adverse reaction caused. The adverse reaction in an elderly person may be more serious than in a younger person and the time of recovery from an adverse reaction may be longer. For example, it may take a considerably longer time to learn to walk following recovery from an Achilles tendon injury caused by fluoroquinolone.

This article discusses adverse reactions in those aged 75 years or more. Vaccines are excluded from the discussion. Since 1973 and until the end of 2006, the adverse drug reaction (ADR) register of NAM has received a total of 2,131 reports of such reactions. During the past 10 years the number of reports has varied between 75 and 122 annually, with reports on serious ADRs accounting for 52–74%.

The majority have concerned the youngest members of that age group, more often involving women (72 %) rather than men (28 %) (Fig. 1). The oldest person involved was a 98-year-old woman who developed serious thrombocytopaenia and petechiae (small capillary haemorrhages of the skin) immediately following the introduction of ofloxazine therapy.

The number of drugs under suspicion totalled 2,331 (one report may include more than one suspected drug). By far the largest number of reports concerned anti-infectives for systemic use (674), followed by cardiovascular system drugs (376), nervous system drugs (366) and drugs for the treatment of musculo-skeletal disorders (296). The reports received are detailed by groups of drugs in the Table. Skin was the most often affected organ (17% of adverse reactions, Fig. 2)

Anti-infectives for systemic use

The majority of reports on anti-infectives were about nitrofurantoin (201), sulphonamide and trimethoprim products (119) and the fluoroquinolones (96). A total of 147 reports on nitrofurantoin described pulmonary adverse reactions. The usual manifestations on chest x-ray were infiltrates or fibrosis associated with the symptoms of dyspnoea and cough, and often combined with fever. If nitrofurantoin therapy is considered necessary in an elderly patient, the symptoms should be carefully monitored and treatment discontinued immediately upon the onset of symptoms indicative of nitrofurantoin lung. Adverse hepatic reactions caused by nitrofurantoin were described in 14 of the reports. Further reports concerned fever as an isolated symptom, and cases of rash, nausea and vomiting.

There were 42 reports on trimethoprim, 33 on the combination of sulfadiazine and trimethoprim and 30 on the combination of sulfamethoxazole and trimethoprim. Of the reports on trimethoprim, 25 concerned various skin symptoms, some of which were serious (3 cases of the Stevens-Johnson syndrome and one of epidermal necrolysis). Changes in the blood count, such as thrombocytopaenia and leukopaenia, were reported on 11 occasions. Adverse reactions caused also by sulphonamide-trimethoprim combination products were expressed mainly in the skin and bone marrow. The period of exposure from the start of the treatment to the discovery of the adverse effect on the bone marrow varied from days to months.

Cephalosporins were reported on in 69, penicillins in 52 and macrolides in 18 reports. Cephalosporins were most commonly reported on owing to diarrhoea associated with the use of cefuroxime (14), often that due to *Clostridium difficile*. Skin symptoms were also common with the use of cephalosporins as well as with penicillin therapy. Half of the adverse reactions caused by macrolides were expressed either in the skin or the liver. Drugs used in the treatment of tuberculosis were reported on 50 times; there were 17 reports each on rifampicin and isoniazide, and 12 reports on ethambutol. The most common effects of ethambutol were on the eyesight (11 reports),

where the most common adverse reaction was optic neuritis with subsequent discontinuation of treatment necessary in order to avoid permanent damage to the sight.

It is interesting to note that oral terbinafine (classified as a dermatological) attracted 15 reports, but other systemic antifungals were only reported on 9 times in all. All adverse reactions caused by terbinafine involved the skin with one report also mentioning a loss of the sense of taste, which is a well-known adverse effect of this drug. The sense of taste is usually restored after discontinuation of the therapy. In the long term this complaint may result in weakening of the nutritional state in the elderly.

Cardiovascular system

ACE inhibitors were reported on 80 times and angiotensin receptor blockers 22 times (including combination products containing diuretics). Medicinal products containing enalapril were responsible for 45 reports and captopril for 21. The most common adverse reactions with these were cough (20), angio-oedema (10) and blood count changes (10) such as agranulocytosis. Diuretics were reported on in 54 reports, most of which being about a combination of hydrochlorodiazide with a potassium-sparing diuretic (19). The majority of the 51 reports received on calcium inhibitors concerned diltiazem (28), the adverse reactions caused by which were almost all about skin symptoms. Beta-blockers attracted 37 reports in all.

Among statins (44 reports in total), atorvastatin was the one most commonly reported on (17) followed by simvastatin (11). Various degrees of muscular (16) and liver (13) reactions were reported as expected. Muscular effects can be difficult to identify in the elderly if both the doctor

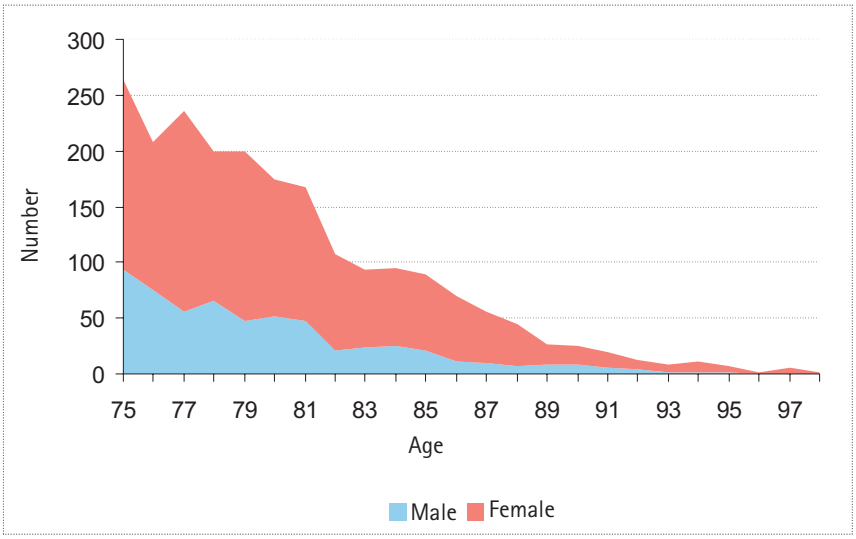

Fig. 1. ADR reports according to age and sex.

and the patient consider them to be associated with the general frailty that comes with age. Interactions increase the risk of statin-induced adverse reactions. For example, the combined use of clarithromycin (500 mg/day) and simvastatin (80 mg/day) in an 85-year-old female was associated with rhabdomyolysis and a 10-fold elevation of the liver enzymes. These drugs were discontinued and the patient recovered. Clarithromycin is a CYP3A4 inhibitor and simvastatin is its substrate. In another case, a 77-year-old male had been prescribed oral fluconazole (150 mg/day) and atorvastatin (40 mg/day), the metabolism of which is mediated by CYP3A4. The patient developed rhabdomyolysis and multiple organ failure, to which he succumbed.

There were isolated cases of drugs used in the treatment of cardiovascular diseases receiving more than 10 reports: amiodarone (15) and methyldopa (15). Digoxin was involved in 9 reports, most of which were about cardiac effects. The effects of digoxin are potentiated in the elderly due to impaired renal function. Several of the important interactions of digoxin are mediat-

ADR reports in the elderly since 1973 divided into drug groups.	*Number of reports*
Anti-infectives for systemic use	*674*
Cardiovascular system	*376*
Nervous system	*366*
Musculo-skeletal system	*296*
Blood and blood-forming organs	*116*
Antineoplastic and immunomodulating agents	*100*
Respiratory system	*45*
Other	*44*
Genito-urinary system and sex hormones	*39*
Sensory organs	*37*
Dermatologicals	*36*
Systemic hormonal preparations (excl. sex hormones and insulins)	*33*
Antiparasitic products, insecticides and repellants	*9*

ed by p-glycoprotein. One report described a 76-year-old male who developed bradycardia, oedema, tiredness and an elevated serum digoxin concentration subsequent to the introduction of itraconazole, a p-glycoprotein inihibitor, in adjunct therapy with digoxin. On discontinuation of itraconazole therapy the digoxin concentration was restored to a normal therapeutic level and the symptoms disappeared.

Drugs affecting nervous system

Among affecting nervous system, most of the adverse reactions reported concerned antiepileptics (58) and antipsychotics (54). The most frequently reported antiepileptics were carbamazepine and pregabalin (both received 16 reports) and phenytoin (14). The majority of these adverse reactions were skin reactions. In addition to epilepsy, pregabalin is also used in the treatment of neuropathic pain. Ten of the adverse reactions it caused involved the nervous system or the psyche; patients for example experienced confusion. It is essential to start treating the elderly with an adequately low dose (e.g. 25 mg of pregabalin twice a day) and to monitor the response and any adverse reactions manifested.

Cholinesterase inhibitors, used in the treatment of Alzheimer's disease, were involved in 41 reports, donepezil in 20, rivastigmin in 16 and galantamine in 5 reports. These reports were mainly about bradycardia or atrioventricular block (10), digestive tract symptoms, such as vomiting and diarrhoea (10) and adverse effects on the liver (3). Reports received on anti-Parkinson drugs numbered 28, most of them on bromocriptine, all 7 reports on which described various fibrotic pulmonary or pleural manifestations.

Antipsychotics attracted a total of 54 reports (most of them, 7, on risperidone) and sedatives and hypnotics a total of 16 (mostly on zolpidem, 5). Opioids were involved in a total of 27 reports with tramadol as the one most commonly reported (15). Nine of the reports on tramadol described adverse reactions on the nervous system and the psyche, such as confusion and hallucinations.

Among antidepressants the one most frequently reported was mianserin, and 38 of its total reports of 46 were about blood count changes, most commonly about leukopaenia of various degrees of severity. Blood count changes were also described in 8 of the total of 17 reports on mirtazapine. The SSRI drugs attracted 29 reports, most of them on citalopram (15) with the most commonly reported single adverse reaction caused being hyponatraemia (4).

Musculo-skeletal system

Among the drugs for the treatment of musculo-skeletal disorders the majority of reports were about anti-inflammatory analgesics, with the biggest group being the coxibs (64 reports). Propionic acid derivatives (ibuprofen, naproxen and ketoprofen) received a total of 38 reports, fenamates 17, indomethacin 15 and diclofenac 13. Of the 20 reports on celecoxib eight involved an adverse skin reaction, and three reports described a gastrointestinal haemorrhage. Celecoxib is structurally a sulphonamide and it must not be prescribed for patients who are allergic to sulpha. Of the 13 reports on etoricoxib three described cardiac failure, and two duodenal ulcer. There were 28 reports received on nimesulide, which has been withdrawn from the market by now, the majority (21) of which were on adverse effects on the liver (during 1999–2002). Stomach or duodenal ulcer was reported three times.

Twenty-six reports were received on allopurinol, and 30 on bisphosphonates. Fifteen of the adverse reactions caused by allopurinol were about various changes in the blood count, most commonly about agranulocytosis, and skin reactions numbered 10. The majority of reports on bisphosphonates involved oral alendronate (16), which most commonly caused oesophageal or stomach ulcers (6) or arthralgia (2). To prevent ulcers in the upper digestive tract, users of alendronate should be carefully instructed to ensure correct intake

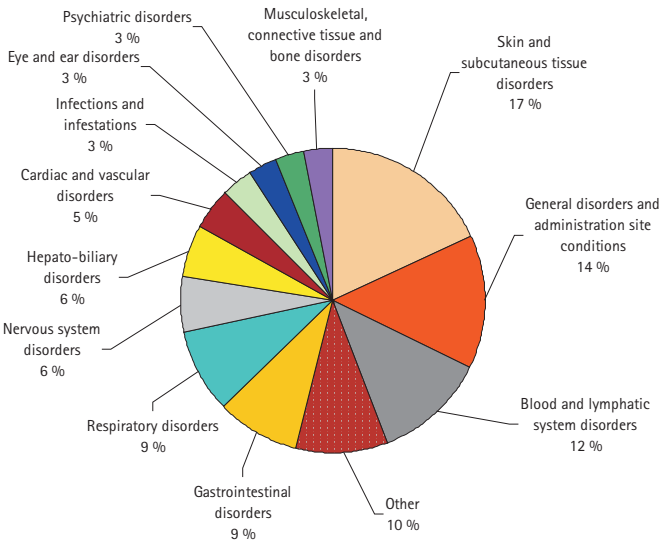

Fig. 2. Reported adverse drug reactions according to SOCs .

of the drug. Five of the seven reports on intravenous zoledronic acid described osteonecrosis (of the jaw), which can impair the quality of life. To reduce the risk, patients should have their teeth examinded and treated before the introduction of zoledronic acid therapy.

Alimentary tract and metabolism

Reports on the drugs for the treatment of diseases involving the alimentary tract and metabolism involved biguanides (27 reports, 17 of which were on metformin and 10 on fenformin, withdrawn from the market since) and sulphonylureas (27). Among the reports on metformin, 10 concerned lactic acidosis, and the majority of reports on sulphonylureas concerned hypoglycaemia. Lactic acidosis is a very rare adverse reaction, but the risk is increased in the elderly and those suffering from malnutrition. Similarly, hypoglycaemia is more readily developed in the elderly with reduced renal function. The hypoglycaemic effect of glibenclamide is also prolonged, because of the accumulation of its active metabolite in the body.

Sulphasalazine was reported on 19 times, the majority of cases were about blood count changes (12) most commonly involving agranulocytosis. Also the majority (11) of the total (18) reports on the metamizole-pitofenone combination product were about an adverse effect on the leukocytes. Because of the risk of agranulocytosis, the necessity for using metamizole ought to be considered carefully. Patients should also be given clear instructions to discontinue their medication and to seek immediately for medical advice when symptoms indicative of agranulocytosis (such as fever, sore throat and malaise) occur.

Proton pump inhibitors were the subject of 15 and H-2 blockers of 12 reports, with the adverse reactions caused by these manifested in various organ systems.

The blood and blood-forming organs

Among drugs used in treatments involving the blood and blood-forming organs, warfarin was reported on 41 times. Of these reports, 33 described some haemorrhages, 12 of which were fatal. The most usual haemorrhages were intracranial (12) or gastrointestinal (8). Of the intracranial haemorrhages four were intracerebral, the risk of which is greater in the elderly receiving warfarin therapy than younger patients. The remaining 8 cases involved subdural haemorrhage, with the common denominator that generally there was no knowledge of any exposure to injury. The most common interaction was an increase in the INR associated with CYP2C9 inhibition and caused by miconazole oral gel (4 reports). The elderly may have difficulties in managing the INR monitoring. One 82-year-old female had continued to take warfarin without INR monitoring, as the intention was to discontinue the medication, but the patient accidentally continued it. As a consequence, she suffered gastrointestinal haemorrhage which ended fatally. There was another case where the excessively high INR value causing a haemorrhage in a 79-year-old female was the result of an “accidental interruption in the INR monitoring”.

Fourteen reports were received on heparins and 30 reports on other coagulation inhibitors, the majority on low-dose acetylsalicylic acid (8), clopidogrel (7) and dipyridamol (6). Alteplase was the object of 13 reports with the most common adverse reaction being intracerebral haemorrhage (8) in patients where the therapeutic indication had been cerebral infarct. One report also described an 80-year-old male who, after having received alteplase for the treatment of myocardial infarction, suffered haemorrhage in the choria of both eyes and was permanently blinded.

Other

Among the reports on anti-cancer drugs and immunomodulators, more than 10 concerned methotrexate (27) and azathioprine (10). In the other drug groups, over 10 reports were received on tamsulosin (20), carbimazole (19), iopromide (17) and verteporfin (11). The most common adverse reaction caused by tamsulosin, used for benign prostate hyperplasia, was IFIS *(Intraoperative Floppy Iris Syndrome)* associated with alpha blockage and making cataract operation difficult (16). All the reports on carbimazole, used for the treatment of hyperthyroidism, were about granulocytopaenia. Iopromide, a computer tomography contrast medium, caused various hypersensitivity reactions, such as rash, nausea and anaphylactic reactions (4). Verteporfin is used as a photosensitising agent in the treatment of retinal degeneration in the elderly and its typical adverse effect is back pain, on which 9 reports were received.

Adverse reactions in the elderly

A 75-year-old male developed insomnia and agitation after the introduction of scopolamine eye drops. The medication was discontinued, but the patient had not yet recovered 5 days later when the report was made. Scopolamine is an anticholinergic which is used in iritis to dilate the pupil. It can cause adverse reactions, such as dry mouth, constipation and micturition problems owing to the muscarine receptor blockage. CNS effects are rare, but possible.

After the introduction of medication with tramadol (100 mg/day), **a 77-year-old female** experienced four nocturnal events of loss of consciousness, once while she was standing up and three times causing her to fall off a chair. She subsequently experienced chest pain and numbness in the left hand. After discontinuation of the tramadol therapy no more attacks occurred. The elderly in particular are sensitive to the adverse effects of tramadol, e.g. dizziness. The treatment should therefore be introduced using a small dose and monitoring the response and adverse reactions; a therapeutic dose lower than that in the younger patients may be adequate (e.g. 50–150 mg/day).

Donepezil therapy introduced in **a 79-year-old male** (at a daily dose of 5 mg) had to be withdrawn after a couple of months of use, because during the entire duration of the therapy the patient (or his wife, rather) was troubled by excessive hypersexuality. The symptom disappeared following discontinuation of donepezil.

A 79-year-old female, who had been using ramipril (at a daily dose of 10 mg) for about three months, started vomiting and developed dizziness and arrhythmia. She was diagnosed as having renal failure and hyperkalaemia. Ramipril was discontinued and the patient was treated with Resonium (a cation exchanger) and fluid therapy. She had not yet recovered at the time of the report being made. ACE inhibitors reduce the renal function in particular if the patient is poorly hydrated, e.g. in association with diarrhoea or a feverish infection. Anti-inflammatory analgesics have the same effect.

An 80-year-old female had used a combination product of metamizole and pitofenone as necessary over a couple of years, when she developed fever. Agranulocytosis with associated septic infection was diagnosed. She was treated with broad spectrum antibiotics and leukocyte growth factors. The patient recovered from angranulocytosis, but her general condition and ability to move about were impaired during hospitalisation. It was not possible to discharge her to her previous care home, and she was consequently transferred to a healthcare centre department for follow-up treatment.

An 80-year-old female was receiving diclofenac for her joint symptoms; the other drugs included clonazepam, alendronate and zopiclone. The patient experienced an event of unconsciousness of some type. Jaundice and elevation of transaminase and bilirubin values were discovered at this stage. Infections and autoimmune diseases were excluded. A liver biopsy finding was indicative of a drug-induced liver damage, the most likely culprit being diclofenac. All therapies were discontinued for a time and a course of prednisolone was introduced. Transaminase and bilirubin values dropped during follow-up after which alendronate therapy was reinstated.

An 82-year-old male was started on zolpidem therapy at a dose of 10 mg administered in the evening. This was followed by the occurrence of nocturnal sleepwalking, hallucinations, odd dreams, and the patient was also said to have “talked strangely”. The symptoms disappeared on withdrawal of the therapy.

A 84-year-old male had used warfarin for atrial fibrillation for several years, when he developed a possible case of “purple toe” syndrome: his toes turned purple and were painful. The symptoms disappeared when warfarin was put on hold owing to a dental procedure, and the symptoms recurred when the medication was reintroduced. The symptoms disappeared when warfarin therapy was withdrawn altogether. The symptoms are thought to have developed during warfarin therapy when the blood seeping into the atherosclerotic plaque sends into the circulating blood small cholesterol emboli which subsequently become impacted in the smaller vessels.

An 85-year-old female was started on trimethoprim therapy (at a daily dose of 300 mg). Following the intake of the first tablet she was feeling unwell and developed fever and experienced confusion. Her level of consciousness dropped and she had to be intubated. She was diagnosed with aseptic meningitis, which recurred when trimethoprim therapy was reintroduced in hospital. After discharge from hospital she was accidentally exposed once more to trimethoprim and was hospitalised again the following morning owing to reduced consciousness. Aseptic meningitis is a well-known, albeit rare, adverse reaction caused by trimethoprim.

An 87-year-old male developed visual hallucinations following the introduction of clopidogrel therapy (at a daily dose of 75 mg). He saw non-existing animals, ants and people. The patient recovered after discontinuation of the therapy. Similar symptoms (confusion and hallucinations) have been described occasionally in patients on clopidogrel therapy.

A 95-year-old male became restless following introduction of ciprofloxacin therapy (at a daily dose of 500 mg). Suicidal behaviour also emerged. The patient was unable to describe why he felt so bad and was so restless. The symptoms disappeared after discontinuation of the medication. Various psychiatric symptoms, such as anxiety, depression, hallucinations and even psychotic reactions, which may be associated with suicidality, are well-known, but luckily rare, adverse reactions induced by fluoroquinolones.

NamWeb – the medicinal product information service is being improved

The Finnish National Agency for Medicines is improving its medicinal product information service. The service is available on NAM's website at *www.laakelaitos.fi* or *www.nam.fi* by clicking in the right hand corner of the first page at *Medicines/ NamWebSearch*.

Information can be found about medicinal products for human use, veterinary medicinal products, herbal medicinal products, products of parallel import and parallel distribution as well as, for example, information about medicinal products with a deleterious effect on driving in traffic. The service provides details of whether a certain medicine is on the market or whether its marketing authorisation has been withdrawn.

The first page of the service provides an additional new search option, by the name of the marketing authorisation holder. The search can also be restricted to include either medicines for human use or veterinary medicinal products exclusively (Fig. 1).

The new service will in future also provide information about the variations made in the marketing authorisations.

The link *Other queries* opens up a page containing information about the following amendments

- trade names
- marketing authorisation holder
- prescription/dispensing condition
- prescription status

The search period can be limited to include a desired period only (Fig. 2).

The links previously provided on the fist page *List medicinal products that may impair the ability to drive and use machines*

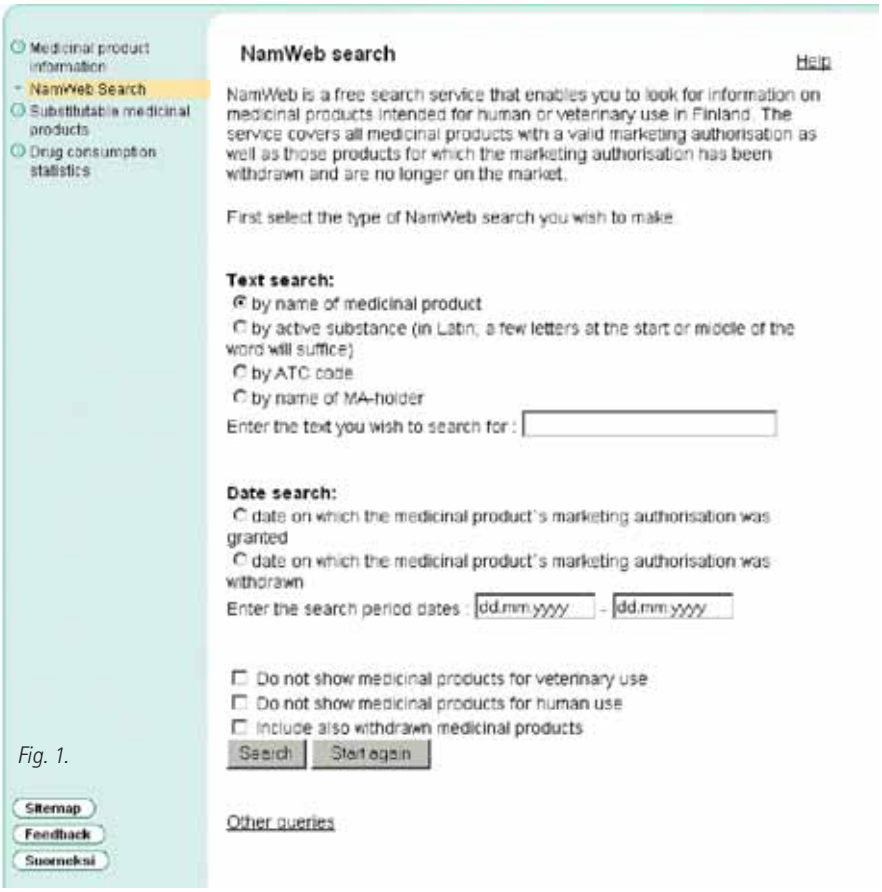

Fig. 1.

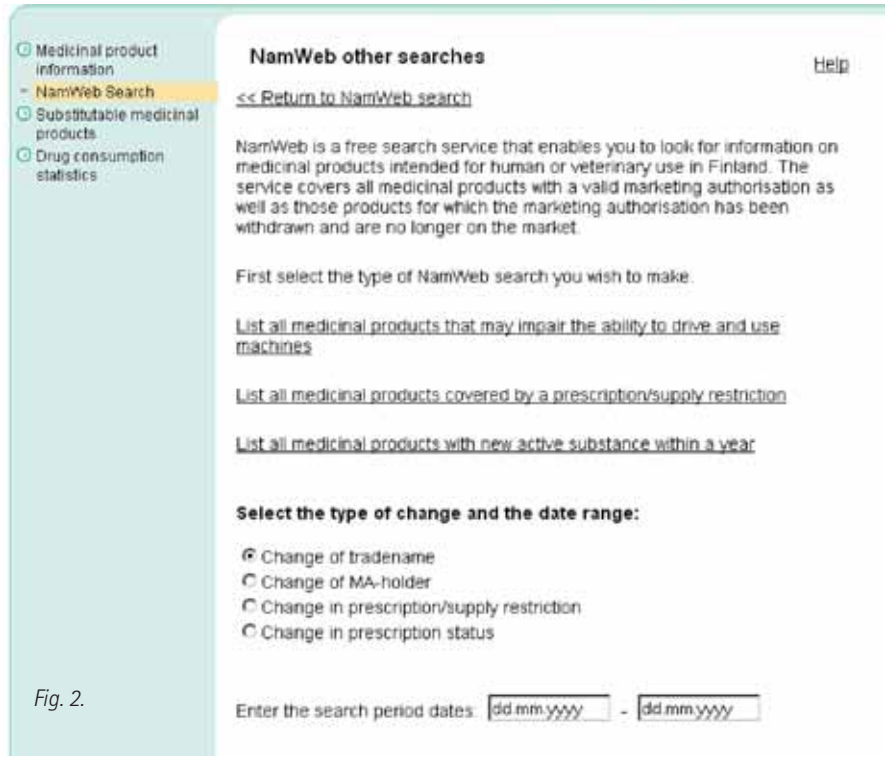

Fig. 2.

– and *List all medicinal products covered by a prescription/dispensing condition* have been moved to the page '*Other queries*'.

This service also allows a search for those medicinal products which contain a new active substance (a new medicinal substance). NamWeb will show a list of those products which have within the past 12 months been granted a marketing authorisation while containing a new active substanceor new medicinal compination. The novelty is shown separately for medicinal products for human use and veterinary medicinal products, according to the ATC Code and first authorisation date of the product.

The following changes have been made concerning medicinal products where information about the individual product is to be found. Following classifications have been added (Figs. 3 and 4)

- Product for parallel distribution
- Herbal medicinal product

The search service shows both the current and the previous names (Fig. 5). The information is found both on the first page by clicking at 'Medicines and on the page for '*Other queries*' when searching for changes of trade names. If the name has not been changed, the section '*Previous trade names*' is blank.

Leila Mälkönen

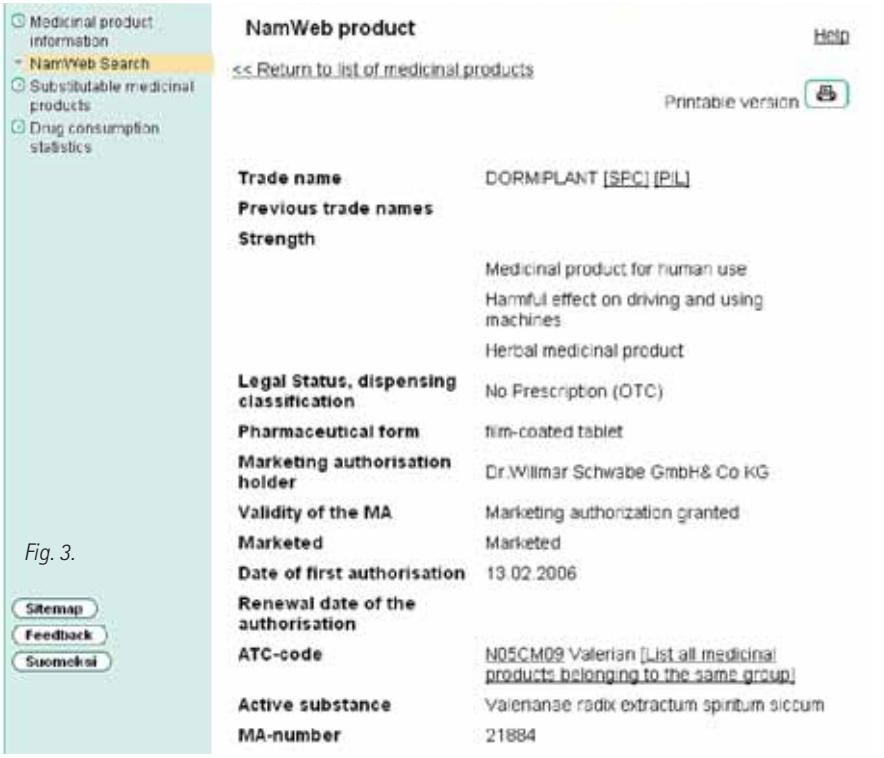

Fig. 3.

Fig. 4.

Fig. 5.