Danish Pharmacovigilance Update

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News in brief

Removal of contraindication for Velcade® (bortezomib) used for the treatment of multiple myeloma

Further to the results of a study of Velcade® involving patients with advanced cancer and varying degrees of hepatic dysfunction, the European Committee for Medicinal Products for Human Use (CHMP) recommends that the contraindication 'severe hepatic impairment' for Velcade® be removed.

Consequently, sections 4.2, 4.3, 4.4 and 5.2 of the summary of product characteristics for Velcade® are to be updated.

For further information, please read the CHMP monthly report (p. 3) *here*.

Interaction updates for Aptivus® (tipranavir) used for the treatment of HIV

The CHMP recommends that co-administration of Aptivus® with alfuzosine as well as with sildenafil, used for the treatment of pulmonary arterial hypertension, be added as a contraindication in the summary of product characteristics for Aptivus®, section 4.3.

Furthermore, the CHMP recommends that colchicine, salmeterol or bosentan should not be used concurrently with Aptivus®, and that section 4.5 should be updated with the following information:

- Co-administration with raltegravir or valacyclovir does not require dose adjustment
- Co-administration with PDE5 inhibitors (medicine used in the treatment of erectile dysfunction) can increase their concentration and result in side effects such as hypotension, syncope, visual changes and priapism.

For further information, please read the CHMP monthly report (p. 3) *here*.

New warnings for Torisel® (temsirolimus) used for the treatment of various types of cancer

Information about the treatment of patients who suffer from hepatic impairment will be added to section 4.4 in the summary of product characteristics for Torisel®.

Among other things, an increased risk of deaths has been observed among patients with moderate to severe hepatic impairment who are treated with Torisel®.

For further information, please read the CHMP monthly report (p. 4) *here*.

New warning for Multaq® (dronedarone) used for the treatment of atrial fibrillation

Warning regarding concomitant use of Multaq® and Pradaxa® (dabigatran, used for prevention of venous thromboembolism in patients who have undergone knee or hip replacement surgery) will be added to sections 4.4 and 4.5 in the summary of product characteristics for Multaq®.

For further information, please read the CHMP monthly report (p. 4) *here*.

Risk of venous thromboembolism from the use of Yasmin® – follow-up

At a meeting in May 2011, the European Pharmacovigilance Working Party (PhVWP) reviewed all available material regarding the risk of venous thromboembolism (VTE) associated with combined oral contraceptives (COCs) containing drospirenone (Yasmin®, Yasminelle® etc.).

The conclusion was that the risk is higher than previously expected and is somewhere between that of 2nd generation COCs (levonogestrel) and 3rd generation COCs (desogestrel/gestoden). The PhVWP recommends that the product information for all drospirenone-containing COCs should be updated to reflect these conclusions.

For further information, please read the PhVWP monthly report from May (p. 1) *here*. Also see Danish Pharmacovigilance Update, May 2011 *here* pp. 3 and 4.

Overall low risk of blood clots from oral contraceptive pills
According to the approved product information of combined oral contraceptives (COCs), the incidence of venous blood clots in women using a low-strength oestrogen COC (<50 µg ethinylestradiol) is 20 in 100,000 for contraceptives with levonorgestrel (2nd generation COC) whereas the incidence of blood clots for COCs with desogestrel/gestodene is 40 in 100,000 (3rd generation COCs). The risk of venous thromboembolism from the use of drospirenone-containing COCs (4th generation pills) is somewhere between the risk of 2nd and 3rd generation pills.

In women not using hormonal contraception, the incidence of blood clots is 5 to 10 in 100,000 women. In pregnant women, the incidence of blood clots is 60 in 100,000 pregnancies. The risk of blood clots is highest in the first 12 months of COC use.

In addition, the risk of developing blood clots increases with age, just as factors such as smoking, positive familial disposition to development of blood clots, hypertension, obesity, prolonged immobilisation as well as certain cardiovascular diseases can increase the risk.

Familial adenomatous polyposis (FAP) should not be treated with celecoxib

The European Medicines Agency (EMA) has recently finalised a review of existing evidence of efficacy and safety of the COX-2 inhibitor celecoxib for the treatment of patients with familial adenomatous polyposis (FAP).

EMA concluded that the benefit of celecoxib in FAP patients does not outweigh the dosis-related risks of e.g. cardiovascular and gastrointestinal side effects from treatment of patients. Therefore, celecoxib should not be used for treatment of FAP.

For further information, please read the CHMP monthly report (p. 5) *here*.

Celecoxib has previously been authorised under the name Onsenal® used to reduce the number of adenomatous intestinal polyps in FAP patients. Onsenal® has now been deregistered. Celecobix-containing medicines are authorised for the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Medicine and dry mouth

Anne Marie Lynge Pedersen, Associate Professor, Dentist, PhD, Department of Oral Medicine, Clinical Oral Physiology, Oral Pathology & Anatomy, Department of Odontology, Faculty of Health Sciences at University of Copenhagen

Medicine is the most common cause of xerostomia (subjective sensation of dry mouth), reduced saliva secretion and changes in saliva composition[1,2]. Furthermore, polypharmacy may strengthen the sensation of dryness of the mouth and the degree of reduced saliva secretion[3,4]. Likewise, the duration of medicine use may impact the degree of salivary gland hypofunction[5].

Dose change or medicine substitution can reduce the risk of xerostomia

It is estimated that more than 1800 marketed medicines from more than 80 different therapeutic groups may cause xerostomia[1]. Medicine-induced xerostomia and reduced saliva secretion are reversible conditions because the effect on the salivary gland function usually ceases when the medicine is stopped. Furthermore, in some cases the adverse reactions can be reduced by changing the dose or substituting the medicine.

Risk of caries, dental erosion, fungal infections and oral mucosal ulcers

Because saliva is very important in keeping the oral cavity healthy, reduced saliva secretion increases the risk of developing caries, dental erosion, fungal infections and oral mucosal ulcers. Furthermore, oropharyngeal functions may be affected, just as the patient's quality of life could be impacted adversely[18]. In factbox 1, you can see a list of symptoms and objective signs of reduced saliva secretion. Treatment options for xerostomia and reduced saliva secretion appear from factbox 2[19].

Factbox 1
Symptoms and objective signs of reduced saliva secretion

- Dry lips, mouth and throat
- Soreness and burning sensation in the oral cavity
- Trouble chewing, swallowing and speaking
- Need for water when eating
- Increased use of candy, pastilles and chewing gum
- Alterations/deterioration of taste perception
- Discomfort when eating spicy and acidic food
- Sensation of stringy and foamy saliva
- Recurring ulcers in the corners of the mouth and in the oral cavity
- Fissure and atrophy of the tongue
- Increased occurrence of oral candidiasis
- Increased caries activity
- Deteriorated sleep quality due to extreme nightly mouth dryness
- Problems with using removable dental prostheses
- Altered eating habits, which could impair the patient's nutritional state
- Soreness and possible swelling of the major salivary glands

Medicine may affect the mechanisms of saliva production at several levels

Thus, some medicines may inhibit the nervous control of saliva secretion in the central nervous system or in the peripheral nervous system, other medicines have a direct effect on the electrolyte and fluid transport mechanisms of the salivary gland cells, and even other medicines may have an indirect effect on saliva secretion through alteration of the body's water and salt balance[1,2].

Medicines with an antimuscarinic/anticholinergic effect, among them anticholinergics for treatment of overactive bladder syndrome and tricyclic antidepressants have a significant inhibiting effect on the nervous control of saliva secretion, centrally as well as peripherally, in the form of competitive inhibition of the postganglionic receptors on the surface of the salivary gland cells[1-3, 6-8].

Also serotonin reuptake inhibitors, SRI, have a corresponding impact on saliva secretion and may cause xerostomia and reduced saliva secretion, albeit to a lesser degree than the tricyclic antidepressants[1-4,9].

Medicines such as antipsychotics, anxiolytics and centrally-acting analgesics affect the saliva secretion mechanism on a central level[1-3,10-12].

Antihypertensives such as α-, β- and calcium-channel blockers usually affect saliva secretion on the peripheral level through interaction with neurotransmitters and peptide binding to specific membrane receptors on the salivary gland cells[1-3, 13,14].

Also antihistamines, in particular 1st generation antihistamines that bind to histamine H_1 receptors, both centrally and peripherally, may inhibit saliva secretion[15].

Medicines such as diuretics have a direct effect on saliva secretion through affecting the body's water and salt balance or a direct effect on the electrolyte and fluid transport mechanisms of the salivary gland cells[16,17].

Factbox 2

Treatment measures in connection with medicine-induced xerostomia and hyposalivation

The patient should first of all be informed of a given medicine's potential xerogenic effect and of the link between reduced saliva secretion and diseases of the oral cavity

If possible, doctors should

- Stop treatment with xerogenic medicines
- Reduce the number of medicines taken daily
- Substitute with a medicine that causes fewer adverse reactions
- Change the dose and time of intake

Refer the patient to a dentist for

- Instructions on good oral hygiene
- Dietary advice
- Oral hygiene control every 3-4 months
- Caries or possibly periodontal treatment
- Fluoride treatment (toothpaste, gel or chewing gum)
- Prosthesis hygiene, control and correction

Stimulation of saliva secretion:

- Sugar-free chewing gum or sugar-free pastilles

Alleviation of mouth dryness symptoms:

- Saliva substitutes (solution, spray or gel)
- Frequent fluid intake

Antimycotics for treatment of oral candidiasis

References

1. Sreebny LM. The causes of dry mouth: a broad panoply. In: Dry mouth – The malevolent symptom: A clinical guide. Eds. Sreebny LM, Vissink A.1. ed. Iowa: Wiley-Blackwell; 2010: 89-127.
2. Jensen SB, Dynesen AW, Pedersen AML. Xerostomi og nedsat spytsekretion: demografiske aspekter og årsager. Tandlægebladet 2011; 115 (5): 366-73.
3. Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AML Associations between labial and whole salivary flow rates, systemic diseases and medications in a sample of elderly people. Community Dent Oral Epidemiol 2010 Oct; 38(5):422-35. doi: 10.1111/j.1600-0528.2010.00554.x.
4. Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AML. Associations between oral and ocular dryness, salivary flow rates, systemic diseases and medications in a sample of elderly people. Community Dent Oral Epidemiol 2010 Nov 10. doi: 10.1111/j.1600-0528.2010.00588.x.
5. Navazesh M,Brigthman VJ, Pogoda JM. Relationship of medical status, medications, and salivary flow rates in adults of different ages. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 81: 172-76.
6. Clemmesen L. Anticholinergic side-effects of antidepressants: studies of the inhibition of salivation. Acta Psychiatr Scand Suppl 1988; 345: 90-3.
7. Dissing S, Hansen HJ, Unden M, Nauntofte B. Inhibitory effects of amitryptyline on the stimulation-induced Ca2+ increase in parotid acini. Eur J Pharmacol 1990; 177: 43-54.
8. Hunter KD, Wilson WS. The effects of antidepressant drugs on salivary flow and content of sodium and potassium ions in human parotid saliva. Arch Oral Biol 1995 Nov;40(11):983-89.
9. Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ 1998 Nov17;159(10):1245-52.
10. Hyttel J, Larsen JJ, christensen AV, Arnt J. Receptor-binding profiles of neuroleptics. Psychopharmacology Suppl 1985; 2: 9-18.
11. de Almeida Pdel V, Grégio AM, Brancher JA, Ignácio SA, Machado MA, de Lima AA, Azevedo LR. Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Jul; 106(1):58-65.
12. Götrick B, Tobin G. The xerogenic potency and mechanism of action of tramadol inhibition of salivary secretion in rats. Arch Oral Biol. 2004 Dec; 49(12):969-73.
13. Nederfors T, Ericsson T, Twetman S, Dahlöf C. Effects of beta-adrenoceptor antagonists atenolol and propranolol on human parotid and submandibular/ sublingual salivary secretion. Dent Res 1994;73: 5-10.
14. Hattori T, Wang PL. Calcium antagonists cause dry mouth by inhibiting resting saliva secretion. Life Sci 2007 Aug 2;81(8):683-90.
15. Kim JH, Park SH, Moon YW, Hwang S, Kim D, Jo SH, Oh SB, Kim JS, Jahng JW, Lee JH, Lee SJ, Choi SY, Park K. Histamine H1 receptor induces cytosolic calcium increase and aquaporin translocation in human salivary gland cells. J Pharmacol Exp Ther. 2009 Aug; 330 (2):403-12.
16. Nederfors T, Twetman S, Dahlof C. Effects of the thiazide diuretic bendroflumethiazide on salivary flow rate and composition. Scand J Dent Res 1989 Dec;97(6):520-7.
17. Atkinson JC, Shiroky JB, Macynski A, Fox PC. Effects of furosemide on the oral cavity. Gerodontology 1989;8(1):23-6.
18. Pedersen AML, Dynesen AW, Jensen SB. Udredning af xerostomi og nedsat spytsekretion. Tandlægebladet 2011; 115 (5): 374-82.
19. Jensen SB, Dynesen AW, Pedersen AML. Behandlingsmuligheder ved nedsat spytsekretion og xerostomi. Tandlægebladet 2011; 115 (5): 384-89.

Simvastatin can cause rhabdomyolysis

The U.S. Food and Drug Administration (FDA) brought an article recently that simvastatin can cause severe muscle injury.

This knowledge is well known and included in the summary of product characteristics of medicines containing simvastatin, which is authorised in Denmark.

There may be an increased risk of myopathy/rhabdomyolysis if simvastatin is used concurrently with the following:

- Itraconazole, ketoconazole, posaconazole (contraindicated with simvastatin)
- Erythromycin, clarithromycin, telithromycin (contraindicated with simvastatin)
- HIV protease inhibitors (contraindicated with simvastatin)
- Nefazodone (contraindicated with simvastatin)
- Fluconazole
- Cyclosporine
- Danazol
- Fibrates (however, not fenofibrate)
- Gemfibrozil
- Amiodarone
- Verapamil, diltiazem or amlodipine
- Colchicine
- Fusidic acid
- Grapefruit juice

For further information, please see the summaries of product characteristics for simvastatin-containing medicines: *www.produktresume.dk* (in Danish only)

Before starting treatment, patients must be informed about the risk of myopathy and instructed to immediately report unexplained muscle pain, tenderness or weakness.

Beware of confusion between Malarone® and Malarex®

The Danish Medicines Agency has received a report from a pharmacy explaining that a doctor confused Malarone® with Malarex®. Malarone® and Malarex® are used to prevent and treat malaria.

The dosage of these two products are very different and therefore, a mix-up could result in overdosing or underdosing.

Adults who are prescribed preventive treatment with Malarex® must take 2 tablets once a week, while adults who are prescribed preventive treatment with Malarone® must take 1 tablet daily.

In connection with prescription, the doctor had mistaken Malarone® for Malarex®, which could have led to an overdose of Malarex® if the mistake had not been discovered by the pharmacy.

Be aware of the dosage when prescribing these products.

Risk of heart malformations in children of mothers treated with an antidepressant of the SSRI type

Epidemiological studies have shown a small increased risk of malformations in the cardiovascular system in newborns of mothers who have taken antidepressants containing fluoxetine or paroxetine in the beginning of pregnancy. In addition, the Danish Medicines Agency has received a few reports of the same type of malformations from treatment with citalopram and sertraline.

Physicians are advised to follow the applicable restrictive recommendations and carefully weigh the risks and benefits of using antidepressants during pregnancy and to consider prescribing the medicines in consultation with specialists within the field (psychiatrist and/or obstetrician).

Studies indicate an increased risk of malformations from treatment with fluoxetine and paroxetine

Epidemiological studies indicate that approx. 2 in 100 newborns of mothers who have been treated with fluoxetine or paroxetine have malformations in the cardiovascular system. In general, malformations in the cardiovascular system of newborns are relatively common and occur spontaneously in approx. 1 in 100 newborns.

As regards the other medicines of the SSRI type, there are no corresponding, unambiguous and valid results from epidemiological studies of the risk of malformations. However, it cannot be ruled out that the other SSRIs (sertraline, citalopram, escitalopram and fluvoxamine) can also cause heart malformations.

Reports of heart malformations from treatment with citalopram and sertraline

The Danish Medicines Agency has, especially lately, received reports of heart malformations in newborns of mothers who had received treatment with the antidepressants citalopram and sertraline.

However, based on the reported incidents, it is not possible to determine if there is a causal relationship between the mother's treatment with SSRI and the observed malformations, or if the malformations occurred randomly.

Further investigations of the link between the use of SSRI and risk of congenital malformation

The Danish Medicines Agency will investigate further whether there is a possible link between SSRI treatment and the risk of congenital malformation and will submit the case to the European Pharmacovigilance Working Party to obtain experience from the other EU member states.

Changed reimbursement rules and reported adverse reactions

In connection with the reassessment in 2010 of reimbursement for a number of medicines for treatment of dyspepsia and certain types of medicines for treatment of cardiovascular diseases, we have looked at possible changes in the reporting of adverse reactions. We have done so to see if the reassessment and the resulting reimbursement changes – and thus patient switches to new products – have impacted the number and type of reported adverse reactions. Although we do not have enough data to draw any definite conclusions at the present time, we can use the data to spot trends in the adverse reactions and reporting pattern.

With regard to medicines used for treatment of cardiovascular diseases, the granting of general reimbursement in April 2010 to losartan, an angiotensin II antagonist, has not surprisingly led to increased consumption. Correspondingly, we saw consumption fall for medicines used to treat cardiovascular diseases which lost reimbursement.

When we review the reporting data for this type of medicine, it is not surprising that the reassessment has also impacted adverse reaction reporting. The reassessment of reimbursement has generated more adverse reaction reports related to the use of losartan, after the time it received general reimbursement. Naturally, this links with the fact that many more users now take losartan-containing medicines.

The adverse reactions reported for losartan-containing medicines are distinct from the adverse reactions reported for other medicines used to treat cardiovascular diseases that most recently lost reimbursement in that more non-serious allergic symptoms and less non-serious symptoms from the nervous system have been reported.

A review of adverse reaction data for a number of medicines for treatment of dyspepsia and certain types of medicines for treatment of cardiovascular diseases after the reassessment of reimbursement in 2010

On 15 November 2010, a number of medicines for treatment of dyspepsia and certain types of medicines for treatment of cardiovascular diseases lost their general reimbursement. As a result, many patients have switched to other medicines. Sometimes, switching to another type of medicine may cause patients to react differently.

At the Danish Medicines Agency, we have monitored the consumption and the reported adverse reactions as regards medicine for the treatment of dyspepsia and cardiovascular diseases before and after the reimbursement changes. We have investigated whether we have received more and/or other types of adverse reaction reports.

Medicines for treatment of dyspepsia

In June 2010, the Danish Medicines Agency decided to remove reimbursement for the more expensive medicines that are used to treat dyspepsia with effect from 15 November 2010. Doctors were informed of the changes in a letter which also encouraged them to switch patients to the less expensive proton pump inhibitors: omeprazole, lanzoprazole and pantoprazole, which maintained general reimbursement.

The more expensive medicines for treatment of dyspepsia, the proton pump inhibitors: rabeprazole and esomeprazole as well as misoprostol-containing medicines lost their general reimbursement on 15 November 2010. Medicines of the antacid type and alginic acid still do not have general reimbursement.

The total prescription sales of all medicines for treatment of dyspepsia in 2010 is shown in figure 1, stated in DDD (defined daily dose).

The consumption pattern for proton pump inhibitors has changed such that there are now more users of proton pump inhibitors that maintained reimbursement and less users of proton pump inhibitors that lost reimbursement. The changes in consumption are traceable already from July 2010, but become more pronounced from November 2010

when the reimbursement changes became effective.
However, throughout the period, the proton pump inhibitors that maintained reimbursement were the most-sold medicines.

Adverse reaction reports of medicines for treatment of dyspepsia

For this type of medicine, only adverse reactions related to the use of proton pump inhibitors have been reported in 2010. The Danish Medicines Agency received a total of 35 reports of suspected adverse reactions, of which six were classified as serious.

Figure 2 shows the number of reports submitted by month.

There are relatively few adverse reaction reports in 2010 for this type of medicine, so there is nothing to suggest that an increased number of adverse reactions has been reported as a result of the reimbursement changes. Almost all of the adverse reaction reports, 29 (83 %), concern proton pump inhibitors which maintained reimbursement and which are the most sold product before and after the reimbursement changes.

Medicines for the treatment of cardiovascular diseases

The reimbursement of medicines for treatment of cardiovascular diseases was also reassessed recently. The first reimbursement changes entered into force in July 2009, when the more expensive ACE inhibitors lost reimbursement. At the same time, reimbursement for angiotensin II antagonists and renin inhibitors and certain dihydropyridine calcium antagonists was reserved for certain patient groups (conditional reimbursement).

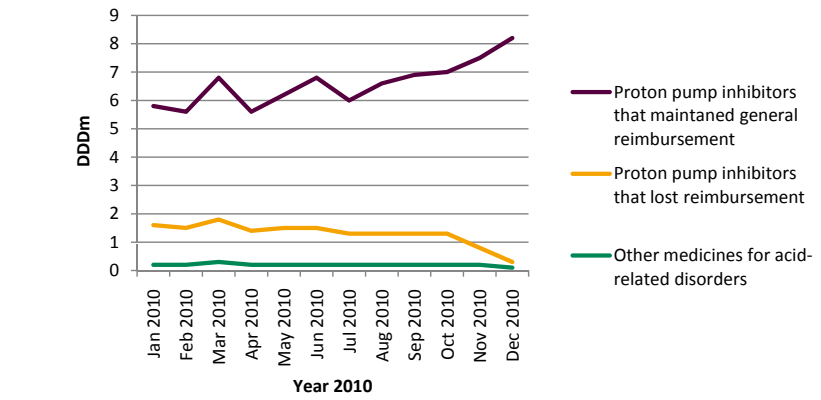

Figure 1. Medicines for treatment of dyspepsia bought on prescription in 2010 in million DDD

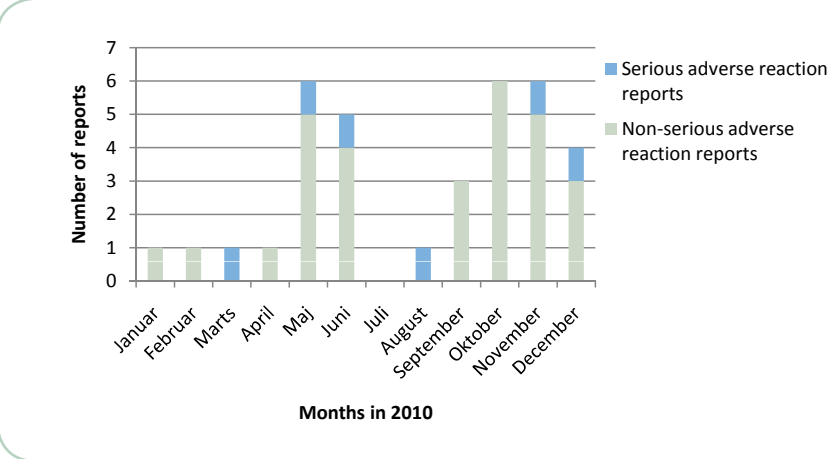

Figure 2. Number of adverse reaction reports in 2010 related to the use of angiotensin II antagonists and renin inhibitors, by serious and non-serious adverse reactions.

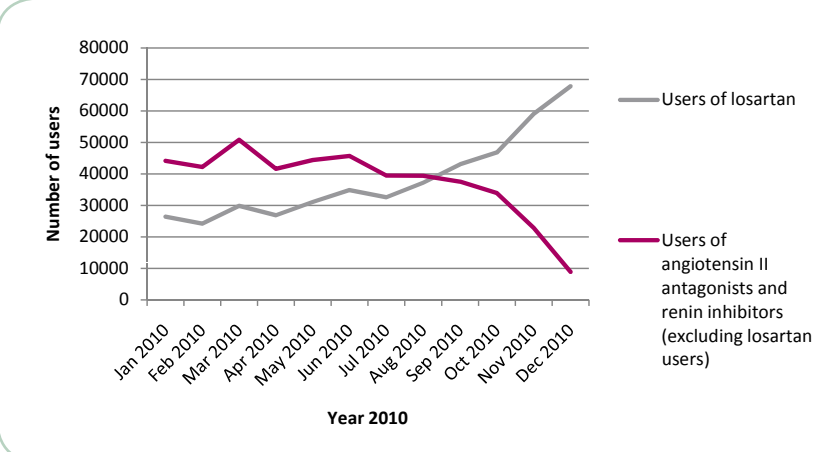

Figure 3. Number of users having redeemed at least one prescription for a medicine within the group of angiotensin II antagonists and renin inhibitors.

Due to patent expiry of the angiotensin II antagonist losartan, many generics were marketed in March 2010 at prices matching the inexpensive ACE inhibitors. This led to an ad hoc reassessment of reimbursement, which implied that:

- losartan-containing medicines were granted general reimbursement as of 16 April 2010
- conditional reimbursement was removed from the other angiotensin II antagonists and renin inhibitors on 15 November 2010.

The consumption for 2010 is stated in the number of users of angiotensin II antagonists and renin inhibitors. See figure 3.

The number of patients treated with losartan increased from approx. 32,000 in July 2010 to approx. 68,000 in December 2010, an increase of 108 percent. The increase in consumption occurred over two periods in particular: from July to October and again from October to end-2010, which coincides with the time when the letter was sent out to doctors in July, and the time when the conditional reimbursement was removed from the other angiotensin II antagonists in November.

The picture is different for the medicines which lost conditional reimbursement. There is a significant fall in the number of patients treated with other angiotensin II antagonists and renin inhibitors from October 2010 until end-2010, during which time the number of patients receiving treatment fell from approx. 34,000 to just under 9,000.

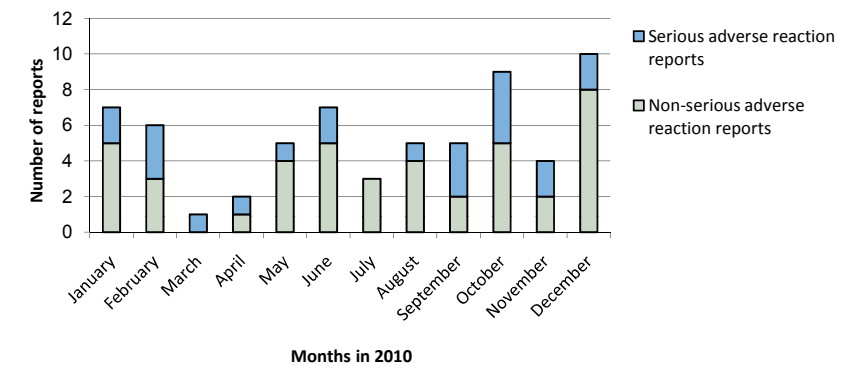

Figure 4. Number of adverse reaction reports in 2010 concerning the group of angiotensin II antagonists and renin inhibitors by serious and non-serious adverse reactions.

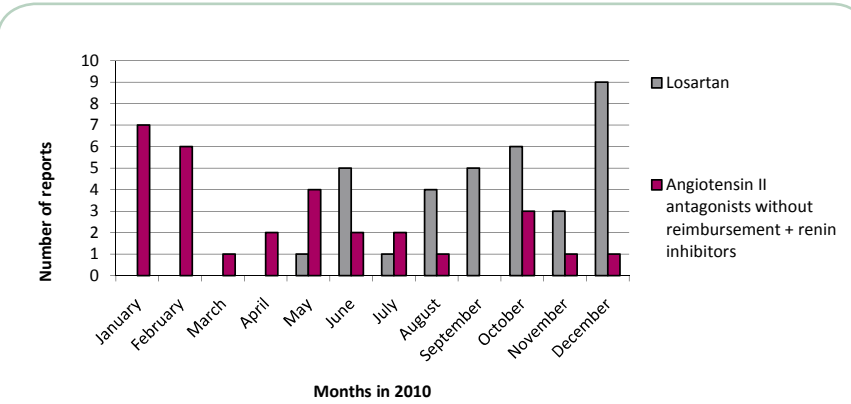

Figure 5. The number of adverse reaction reports in 2010 broken down on losartan with general reimbursement and the other angiotensin II antagonists and renin inhibitors without reimbursement.

Adverse reaction reports of medicines for cardiovascular diseases

In 2010, the Danish Medicines Agency received a total of 64 reports of suspected adverse reactions concerning other angiotensin II antagonists, of which 22 were classified as serious. Figure 4 shows the number of reports submitted by month in 2010.

The number of adverse reaction reports spreads evenly, yet with a slight increase in October-December, when the reimbursement changes became effective.

However, the number of reports is too small to draw any conclusions. The reports spread evenly over the entire period, ranging from one to four reports a month.

Figure 5 breaks down the 64 adverse reaction reports of losartan-containing medicines and the group of angiotensin II antagonists (excluding losartan) and renin inhibitors without reimbursement.

As can be seen from figure 5, a change in the number of reported adverse reactions has taken place after May 2010 when losartan was granted general reimbursement.

Until May, all adverse reaction reports on medicines for the treatment of cardiovascular diseases concerned the use of the other angiotensin II antagonists and renin inhibitors without reimbursement.

In the period starting in May 2010, the first adverse reaction reports involving losartan were submitted. From August 2010 until end-2010, the reported adverse reactions predominantly concerned the use of losartan.

The rise in the number of reports submitted for losartan is not surprising because losartan consumption increased more than two-fold during the same period. It is always important to take consumption into account when looking at the number of adverse reaction reports. Also, whenever there is special focus on a particular type of medicine, e.g. in connection with reimbursement changes, it will always rub off on the reporting of adverse reactions.

The most significant difference between the reports submitted for losartan, which received general reimbursement, and the reports submitted for other angiotensin II antagonists and renin inhibitors without reimbursement, is that losartan more often generates reports of adverse reactions involving symptoms of the skin, e.g. rash and itching and symptoms of the airways, e.g. dry throat and cough than do the other angiotensin II antagonists and renin inhibitors.

Conversely, losartan has generated fewer reports of adverse reactions with symptoms from the nervous system, such as sleeplessness, dizziness and headache than the other angiotensin II antagonists have. All the mentioned adverse reactions are already known and non-serious adverse reactions of angiotensin II antagonists.

The Danish Medicines Agency will continue to follow the reporting trends and monitor any changes in the number and type of reported adverse reactions for medicines used for the treatment of dyspepsia and for the treatment of cardiovascular diseases.

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