LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

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DANISH PHARMACOVIGILANCE UPDATE

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News from the EU

News from the Danish Medicines Agency

Short news

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed at the PRAC meeting in December 2015 concern the following products:

- **Hormone replacement therapy medicinal products containing oestrogens or combined oestrogens-progestagens** – Increased risk of ovarian cancer
- **Human fibrinogen, human thrombin (Tachosil)** – Intestinal obstruction

See EU's list of recommendations on safety signals: *PRAC recommendations on signals December 2015* *as well as the* *Danish translations for the product information*.

Safety monitoring following switch from Gardasil® to Cervarix® as HPV vaccine in the childhood immunisation programme

Since HPV vaccination was introduced into the Danish childhood immunisation programme in 2009, the Gardasil® HPV vaccine has been used. As of 1 February 2016, all girls offered HPV vaccination in the childhood immunisation programme will, however, be started on the Cervarix® HPV vaccine. The switch is made in pursuance of the statutory vaccine tender.

Switch from Gardasil® to Cervarix®

Like Gardasil®, Cervarix® offers protection against the two oncogenic HPV types 16 and 18, which cause 70% of all cervical cancer cases. The protection against cervical cancer offered by Cervarix® and the vaccine's known adverse reactions are comparable to Gardasil®, but unlike Gardasil®, Cervarix® offers no protection against genital warts (HPV types 6 and 11).

Suspected adverse reactions to the Cervarix® vaccine subject to stricter reporting requirements

As the Cervarix® vaccine has never before been used in the Danish childhood immunisation programme, the Danish Medicines Agency, DKMA, has subjected the vaccine to stricter reporting requirements. This means that any suspected adverse reactions to the vaccine must be reported by doctors (dentists and midwives). Gardasil® too was subjected to stricter reporting requirements when introduced in the immunisation programme in 2009.

Increased monitoring continues

The DKMA also encourages other healthcare professionals, patients or their representatives who suspect that they themselves or their patients have had adverse reactions to the HPV vaccine to report them to the DKMA. When submitting an ADR report, it is important to name the HPV vaccine given and indicate the batch number if this is possible.

You can read more about the changes affecting HPV vaccination in the childhood immunisation programme in the latest issue of EPI-NEWS from the SSI: *Novel HPV vaccine in the childhood vaccination programme*.

The list of medicines presently subject to stricter reporting requirements is available from the DKMA website: *Medicines with stricter reporting requirements for doctors, dentists, veterinarians and midwives*.

ADHD medicines and cardiovascular adverse reactions

Over the past couple of years, the DKMA has received three ADR reports of deaths in connection with methylphenidate treatment. All three reports describe suspected cardiovascular effects as having caused the deaths. In addition, we have received one ADR report about a child who, while being treated with Concerta®, suffered a cardiac arrest leading to permanent injuries. The child survived, but had a pacemaker implanted.

The literature also describes several cases of sudden death and acute myocardial infarction observed in users of ADHD medicine. A national cohort study concludes that cardiovascular symptoms are twice as likely in children and adolescents who use ADHD medication compared to non-users (Dalgaard et al. 2014). In this study, arrhythmia was the most frequently observed cardiovascular effect.

Consequently, we have sharpened our focus on cardiovascular adverse reactions of ADHD medicines and have recently completed a review of all suspected cardiovascular effects reported with ADHD medicines.

Until July 2015, the DKMA has received a total of 845 reports of suspected adverse reactions associated with an ADHD drug (methylphenidate, atomoxetine, lisdexamfetamine and dexamfetamine). Cardiovascular adverse reactions were suspected in 103 of these reports. We review the 103 ADR reports in this article. Of the 103 ADR reports, 66 were submitted in the past five years[1].

Review results

The vast majority of the suspected cardiovascular effects reported with use of ADHD drugs covers known adverse reactions described in the summaries of product characteristics (SPCs). Most of the patients involved have since recovered from the adverse reaction, and the medicine used was stopped in most cases.

The review suggests that more and more people are treated for longer periods of time: The total number of medicated persons has increased or stayed stable (depending on age group) in the last couple of years, but the number of new users has dropped markedly in recent years. It may suggest that more children continue treatment into adulthood.

Please pay attention to the following:

- **Contraindications related to cardiovascular adverse reactions according to the SPCs:**
  - **Ritalin (methylphenidate):** Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies,

[1] After the above review of ADR reports, we have received a further three reports of suspected adverse reactions involving use of ADHD medicines. Two of these reports describe patients who experienced symptoms such as chest pain and palpitations after treatment with an ADHD drug. The third ADR report describes a child who, after treatment with lisdexamfetamine and sertraline, had three reversible cerebral infarcts. At discharge, the child had no neurological deficits. When investigating these events, no infarct-inducing causes were found, but they were suspected to be an adverse reaction to either Elvanse, Sertralin or a combination.

myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).

- **Adjuvanz/Elvanse (lisdexamfetamine):** Symptomatic cardiovascular disease, advanced arteriosclerosis. Moderate to severe hypertension.

- **Attentin (dexamfetamine):** Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).

- **Strattera (atomoxetin):** Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders. Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and disorders caused by the dysfunction of ion channels. Severe cerebrovascular disorders may include cerebral aneurysm or stroke.

- **Pre-treatment screening**
  - Prior to prescribing ADHD medication, it is necessary to evaluate the patient's cardiovascular status, including blood pressure and heart rate. An appropriate medical history must be taken, covering medications, past and present medical and psychiatric disorders or symptoms, family history of sudden cardiac or unexplained death (see the SPC).

- **Ongoing monitoring of the patient's cardiovascular status**
  - Blood pressure and pulse should be recorded at each adjustment of dose and then at least every six months.
  - Patients should be informed of symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during medical treatment of ADHD. A patient experiencing any of these symptoms should seek medical advice immediately and be evaluated by a cardiologist.

Use of ADHD medication and review of the 103 reports of use-related suspected cardiovascular adverse reactions

Number of users of ADHD medicines

The number of persons on ADHD medication has increased markedly from 2008 to 2014 (see figure 1). However, the number of persons treated with either methylphenidate or atomoxetine has stayed stable since 2012. Most patients treated medically for ADHD use methylphenidate, which is predictable as methylphenidate is the first-line agent in medical treatment of ADHD.

Lisdexamfetamine was not marketed before April 2013, and the number of users has increased steadily ever since.

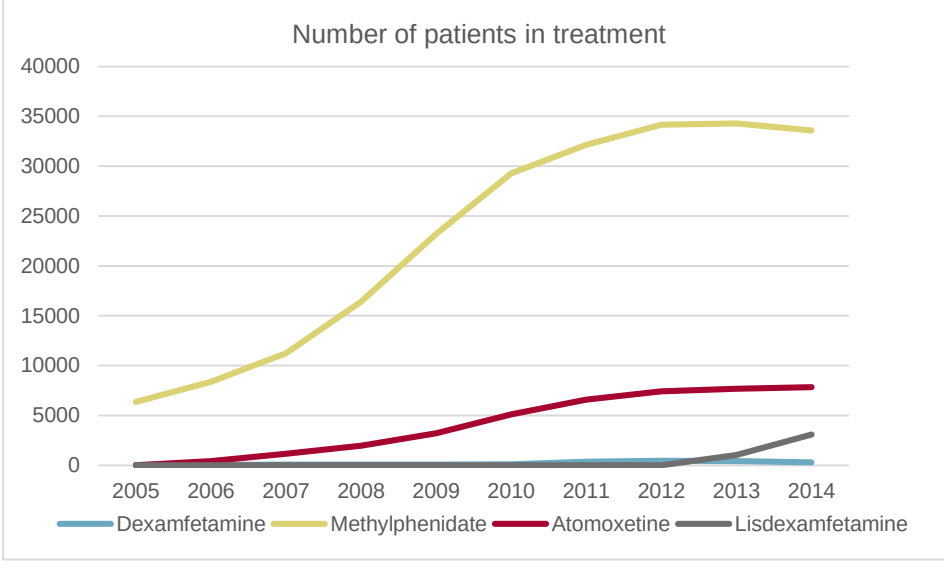

Figure 1. Number of persons treated medically for ADHD from 2005-2014 (Register of Medicinal Product Statistics, Danish Health Data Authority).

The highest increase in use of ADHD medication is recorded in the age groups of 20-39 and 40-64 years, but the number of users aged 5-9 years has decreased since 2010 (figure 2).

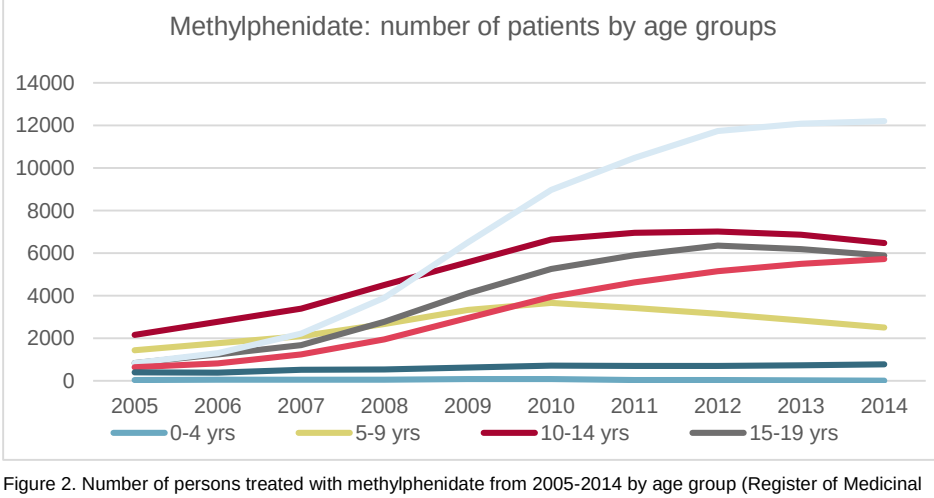

Figure 2. Number of persons treated with methylphenidate from 2005-2014 by age group (Register of Medicinal Product Statistics, Danish Health Data Authority)

The same trend is recorded for atomoxetine, showing an increase in the number of adult users aged 20-39 years.

The number of dexamfetamine users is low[2] and has declined across all age groups since 2010.

The number of lisdexamfetamine users has increased across all age groups from 5-64 years.

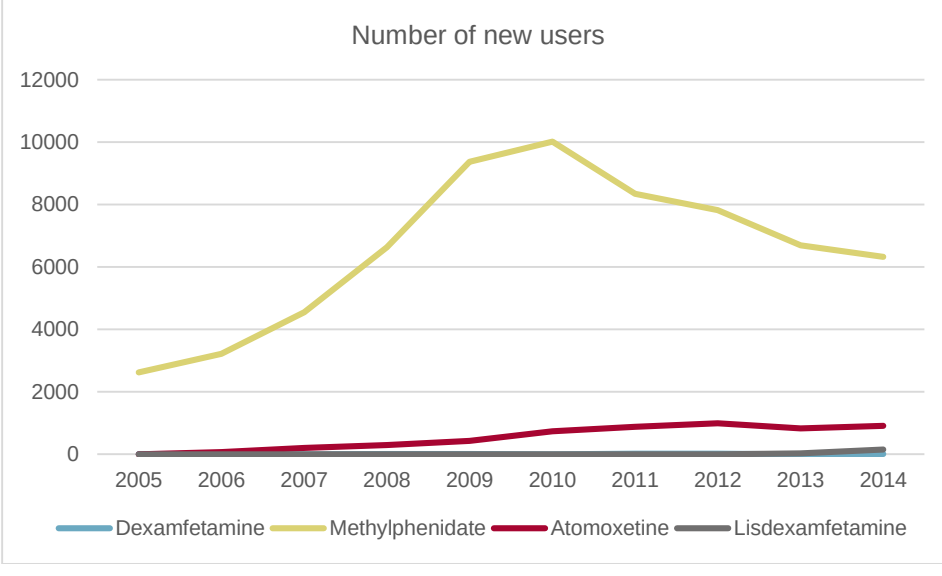

Figure 3. Number of new users treated with ADHD medication from 2005-2014 (Register of Medicinal Product Statistics, Danish Health Data Authority)[3].

Figure 3 shows the number of new users by ADHD medicine. While the number of new methylphenidate users fell from 10,023 in 2010 to 6,322 in 2014, the number of new atomoxetine users grew moderately from 732 in 2010 to 914 in 2014. In addition, 151 brand new lisdexamfetamine users appear from 2013 to 2014.

Figure 2 shows that the number of methylphenidate users increases until 2014 in the 20-39 age group. Conversely, figure 4 shows a drop in the number of new users in the same age group from 2010-2014. It may suggest that more patients are treated long-term with methylphenidate.

The number of new dexamfetamine users is minimal, ranging between 2-23 users annually.

[2] In September 2014, a new dexamfetamine-containing ADHD product (Attentin) was authorised. Before authorisation, dexamfetamine was available as magistral preparations.

[3] New users of an ATC code are defined as persons who have never previously redeemed a prescription for a medicine with the ATC code in question.

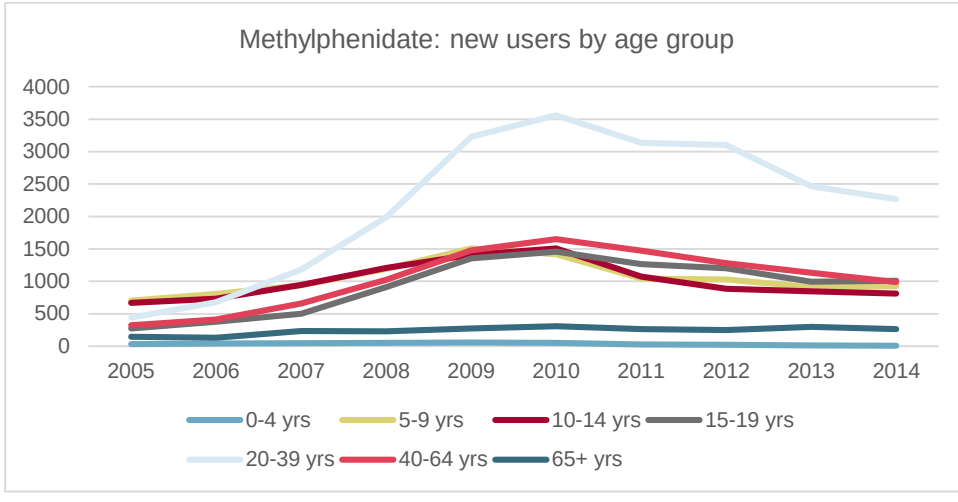

Figure 4. Number of new methylphenidate users by age group from 2005-2014 (Register of Medicinal Product Statistics, Danish Health Data Authority).

Since 2010, the number of new methylphenidate users has fallen across all age groups under 65 years (see figure 4). The figure reveals that the increase from 2005 to 2010 is explicit in the age group of 20 to 39 years.

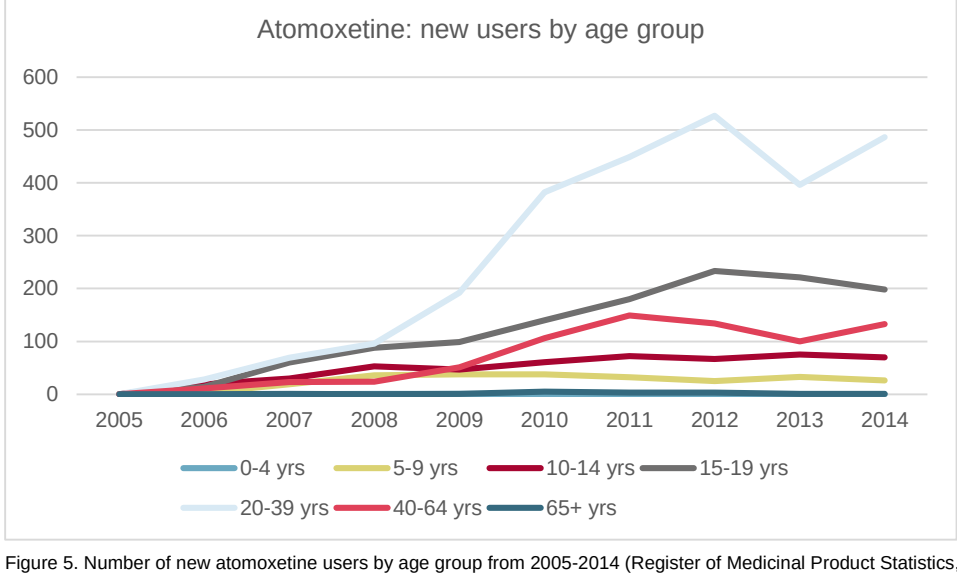

Figure 5. Number of new atomoxetine users by age group from 2005-2014 (Register of Medicinal Product Statistics, Danish Health Data Authority).

Up until 2012, an increase is recorded in the number of new amoxetine users aged 15-19 years and 20-39 years. Then the number of users falls or stabilises (see figure 5). For the other age groups, the number of new users stays more or less stable over the period.

The number of new lisdexamfetamine users is increasing for all age groups under 65 years. The number of new dexamfetamine users is minimal, and further analyses on these age groups is not possible.

Review of ADR reports of cardiovascular adverse reactions related to ADHD medicine

As mentioned earlier, we received a total of 103 reports of suspected cardiovascular effects related to ADHD medication. The ADR reports break down as follows: methylphenidate (69), atomoxetine (24), lisdexamfetamine (9) and dexamfetamine (1)[4]. Out of the 103 ADR reports, 66 were submitted in the past five years.

Table 1. Number of ADR reports of cardiovascular adverse reactions by age and ADHD product

	Number of ADR reports of cardiovascular effects		
Age group	**Methylphenidate**	**Atomoxetine**	**Lisdexamfetamine**
0-4	0	0	0
5-9	9	4	1
10-14	12	2	2
15-17	10	8	1
Total number of children/adolescents: 50 (50/103 = 49%)			
18-39	16	4	3
40-65	9	1	0
66+	2	0	0
Total number of adults: 35 (35/103 = 34%)			
Age unknown (18/103 = 17%)	11	5	2

Although most of the ADR reports related to ADHD medication concern children and adolescents (49%) (table 1), the highest number of users is recorded in the adult segment, especially in the recent years. The reason could be that there has been more focus on medicated children and adolescents, or because cardiovascular symptoms in adults are not commonly perceived as adverse drug reactions since these particular symptoms tend to increase with age. In other words, such adverse reactions are easier to miss.

Table 2 shows the most frequently reported cardiovascular adverse reactions related to use of ADHD medication.

[4] This single ADR report about dexamfetamine is not mentioned in the subsequent tables.

Table 2. The most frequently described cardiovascular adverse reactions in the 103 ADR reports

Adverse reaction described in the ADR report	Number of adverse reactions		
	Methylphenidate	**Atomoxetine**	**Lisdexamfetamine**
Palpitations/increased heart rate/ Tachycardia[5]	32	15	10
Hypertension/increased blood pressure and blood pressure fluctuations	5	1	1
Atrial fibrillation	5	-	-
Myocardial infarction	7	-	-
Angina pectoris	3	3	-
Cardiac arrest*	3	-	-
Cyanosis	3	1	-
Intracardial thrombosis	2	-	-
Ventricular fibrillation and ventricular extrasystoles	2	1	-
Reduced ejection fraction	2	-	-
Paleness	2	-	-
Thrombosis	2	1	-
Redness	-	2	-
Chest pain	-	-	3

* One patient dies – the patient's underlying disease is suspected to be the cause. Two patients are resuscitated, and ADHD medication is suspected to have caused the myocardial infarction.

Only one ADR report describing dexamfetamine has been submitted to the DKMA. It describes a man who, after switching to dexamfetamine, was acutely admitted to hospital with chest pain radiating down the left arm. The patient was operated on, implanting two stents, and has recovered. Prior to starting treatment, the patient had angina pectoris. Hypersomnia was noted as the indication for treatment with centrally-acting medicine.

The majority of the reported suspected cardiovascular adverse reactions are known

The vast majority of the suspected cardiovascular effects reported to the DKMA are known adverse reactions described in the SPCs for each individual ADHD product. It appears, among other things, that the medicine is associated with cardiovascular events with increases in blood pressure (on average 1-4 mm HG) and heart rate (on average 3-8 bpm). These symptoms generally do not have clinical relevance in the short term, but the long-term effects have not been studied.

[5] The adverse reactions are translated from Danish as they appear in the reports.

Indications reported for the 103 patients' treatment with ADHD medication
For the majority of patients, the indication was either ADHD: (methylphenidate (47), atomoxetine (20), lisdexamfetamine (7) and dexamfetamine (0)), or unknown: (methylphenidate (16), atomoxetine (1), lisdexamfetamine (1) and dexamfetamine (0)).

Polypharmacy
A small proportion of the patients were, according to the ADR reports, treated concomitantly with non-ADHD medication (such as antipsychotics, antidepressants and melatonin). We did not find anything to suggest that patients on polypharmacy developed more severe adverse reactions than patients who received no other medication concomitantly.[6]

Long-term use of ADHD medication
The safety and effect of long-term use (more than 12 months) of ADHD medicine have not been studied systematically in controlled trials. Therefore, patients in long-term treatment (more than 12 months) should be monitored closely and continuously as indicated in the SPCs.

A doctor who chooses to use ADHD medicine for extended periods (over 12 months) should periodically re-evaluate the benefit of the drug for the individual patient. The patient's problems/functioning should be evaluated during periods without pharmacotherapy.

According to the ADR reports, less than 20% of patients received treatment for more than one year (1-12 years). The patients who were treated for extended periods had more severe cardiovascular adverse reactions than those who received treatment for less than a year.

Conclusion

The vast majority of the suspected cardiovascular effects reported in relation to treatment with ADHD medicine and described above are known adverse reactions described in the SPCs. Most of the affected patients have since recovered from the adverse reaction, and the medicine used was stopped in most cases. The DKMA will continue to monitor ADR reports of cardiovascular effects and other adverse reactions of ADHD medication.

[6] Information about co-administered medication is not mandatory in ADR reporting, which may render the information incomplete.

Healthcare professionals to observe new rules on the monitoring of biological medicines and biosimilars

As of 1 January 2016, new rules entered into force regulating the recording in patient records and reporting of adverse reactions of biological medicines (including biosimilars) affecting healthcare professionals.

Attention is drawn to the following:

1. Patient records should include information about the name and batch number of a prescribed biological medicine which appears on a list prepared by the Danish Medicines Agency. The list is made available to the Danish Patient Safety Authority, which publishes it on its website[7]. The entry in patient records of prescribed biological medicines should otherwise continue as before, i.e. to the extent considered relevant and necessary for the treatment of the individual patient.

2. ADR reports from healthcare professionals should as far as possible include information about the medicine's name and batch number when the ADR report concerns a biological medicine appearing on the list prepared by the Danish Medicines Agency and published on its website[8].

List of biological medicines covered by the new rules
The rules apply only to those biological medicines appearing on the list published on the DKMA website *www.dkma.dk* and the website of the Danish Patient Safety Authority *www.stps.dk*.

[7] Please refer to the Danish executiver order no. 1606 of 8 December 2015 amending the executive order on authorised healthcare professionals' patient records (record keeping, storage, dissemination and transfer etc.). The new provision regulating the requirements for patient records appears in section 10(4) of the executive order on authorised healthcare professionals' patient records.

[8] Please refer to the Danish executive order no. 1823 of 15 December 2015 on reporting of adverse reactions of medicinal products, etc. The new provision regulating name and batch number appears in section 7(2) of the executive order.

The list is dynamic and will be updated continually. The list presently contains the following medicines:

Product name	Active substance
Retacrit®	Erythropoietin
Eprex®	Erythropoietin
Bemfola®	Follitropin alfa
Gonal-F®	Follitropin alfa
Omnitrope®	Somatropin
Genotropin®	Somatropin
Zarzio®	Filgrastim
Nivestim®	Filgrastim
Neupogen®	Filgrastim
Remicade®	Infliximab
Inflectra®	Infliximab
Remsima®	Infliximab

The DKMA's list of biological medicines subjected to the rules on recording of batch number and product name in the patient record, and the rules stipulating, to the extent possible, to provide the name and batch number of a medicine when reporting suspected adverse reactions of any of the medicines appearing on the list.

Background leading to new rules

As patents for biological medicines are running out, more and more biosimilars are developed. The new rules are to contribute to a targeted and product-specific surveillance of biological medicines and biosimilars to ensure a confidence-building and safe care of patients whenever these medicines are involved.

Link to the DKMA's list of biological medicines subjected to the new rules: *List of biological medicines and biosimilars*.

Intrauterine exposure to paracetamol and effect on fertility

The results of a new Danish study[9] suggest that intrauterine exposure to paracetamol and aniline in female mice may impair fertility.

The study observed a shortening of the anogenital distance and reduction of primordial follicles in female mice exposed intrauterine to paracetamol. Exposed female mice also had fewer full-term pregnancies than the control arm at the age of 6 and 10 months. The strength of the study is impacted by small group sizes in several of the observations as well

[9] Holm BJ et. al, Intrauterine exposure to paracetamol and aniline impairs female reproductive development by reducing follicle reserves and fertility, Toxicol. Sci. (2016) January 5, 2016, doi: 10.1093/toxsci/kfv332

as uncertainties about the significance of, for example, anogenital distance in female mice. The doses used in the study are comparable to the recommended therapeutic doses of paracetamol in humans, but the actual exposure in the animals have not been measured.

Difficult to transfer results to humans – no changes to the recommendations for use during pregnancy

It is difficult to assess the clinical relevance of the results in humans. For one thing, there are relevant differences between the metabolism in humans and mice. For another, the study is small. It is therefore not possible to make recommendations about pregnant women's use of paracetamol based on this study.

Based on the overall knowledge about paracetamol-use during pregnancy, the recommendations remain unchanged.

The DKMA's recommendations for use of painkillers during pregnancy

- It is generally recommended that women take as little medicine as possible during pregnancy.
- Women who experience mild and/or short-term pain during pregnancy should as far as possible opt for non-medical treatment.
- Paracetamol is still recommended as first-line treatment during pregnancy when medical treatment is necessary for pain and fever. The medicine should always be used at the lowest effective dose for as short a time as possible.
- Pain-relieving medicines of the NSAID type should, due to the risk of malformations, be used cautiously in the 1st and 2nd trimesters of pregnancy and should not be used in the 3rd trimester of pregnancy due to the risk of bleeding and circulatory disturbances in the child.

Further investigations

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee, PRAC, most recently assessed the use of paracetamol during pregnancy in 2014 at which time it concluded to maintain the current recommendations.

The DKMA now forwards the results of this new study to the relevant members of the PRAC.

SSRIs and tricyclic antidepressants, dry mouth and oral cavities

Lately, the DKMA has been contacted frequently by citizens who have experienced tooth problems while using SSRIs.

Known adverse reaction of SSRIs
Dry mouth is a known adverse reaction of all SSRIs and tricyclic antidepressants as the medicine has a significant inhibiting effect on the nervous regulation of salivary secretion. It is also well-known that dry mouth increases the risk of dental caries and thus cavities. Saliva plays a central role in keeping the oral cavity healthy. When salivary secretion is reduced, the risk increases of developing caries, dental erosion, fungal infections and ulcers of the oral mucosa.

Therapeutic measures in drug-induced dry mouth:

- The patient should be informed that the medicine can give dry mouth and advised about the connection between reduced salivary secretion and oral cavity disorders.
- If possible, treatment with medication inducing dry mouth should be stopped.
- If possible, the daily medical intake should be reduced.
- If possible, the medication should be replaced by an alternate product not inhibiting salivary secretion.
- If possible, the dose and time of intake should be changed.

Referral to a dentist for:

- Instructions in good oral hygiene
- Dietary advice
- Oral hygiene check-up every 3-4 months
- Caries and possibly periodental treatment
- Flouride therapy (tooth paste, chewing gum)
- Denture hygiene, control and adjustment

Stimulation of salivary secretion:

- Sugar-free chewing gum or tablets

Alleviation of dry mouth symptoms:

- Saliva replacement products (solution, spray or gel).
- Frequent fluid intake

For further information, please see the article about medicine and dry mouth in *Danish Pharmacovigilance Update, 16 June 2011*.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Viekirax** (ombitasvir, paritaprevir, ritonavir) with/ without Exviera (dasabuvir) no longer recommended in Child-Pugh B patients – Sent out 4 January 2016.
- **Gilenya** (fingolimod) risks associated with effects on the immune system – sent out 25 January.
- **Angicor** or **Ikorel** (nicorandil) – should not be used as first-line treatment of angina pectoris – risk of ulceration and development of complications – sent out 17 December 2015.
- **Tarceva** (erlotinib) – no longer indicated as first-line maintenance treatment in patients without an epidermal growth factor receptor (EGFR) activating mutation – sent out 14 January 2016.

The DHPCs are available in Danish at the DKMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

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