LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

DKMA Update is an electronic newsletter intended for anyone who work with medicines either clinically or in the pharmaceutical industry or the retail industry and people who would like to gain an insight into our work and get the most recent updates on medicines and medical devices. The newsletter contains information about current medicine issues, the most recent safety updates and reimbursements.

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Editorial: Happy New Year from the Danish Medicines Agency

Thomas Senderovitz

The Danish Medicines Agency is wishing everyone of our cooperation partners a truly merry Christmas and a prosperous New Year!

In 2017, we started the first year of our five year strategy with the vision of positioning the Danish Medicines Agency among Europe's best in class.

As we enter a new year, we also look back at several strong results obtained for the benefit of both human and animal health as well as growth in Denmark. We are delighted about this!

Thank you for your collaboration throughout 2017 – I look forward to continuing work in 2018!

The most significant points include the various initiatives we started to reduce our assessment times – work goes on in 2018. We also commenced a fruitful collaboration with the China Food and Drug Administration, and on our home ground we succeeded in setting the framework for both the medicinal cannabis pilot programme and the development scheme for the cultivation of cannabis.

Our commitment in the European network has increased, and we work determinedly to get more rapporteurships and prepare for the new clinical trials and medical devices regulations. Last but not least, we contributed to putting Danish life science on the map in connection with the vote on the new location of the European Medicines Agency (EMA).

Editorial

We may not have crossed the finish line first, but we are very proud of Denmark's distinguished third place, which shows the strength of Copenhagen as a life science cluster.

We are looking forward to continuing our good results in 2018 – we will still be working determinedly to improve our assessment times, carry out more inspections and laboratory controls, and we will contribute our expertise to turn Denmark into a leading life science nation.

At the European level, many exciting challenges will be waiting when we and our collaboration partners come together and the real work after Brexit begins. Many tasks, stakeholders and roles in the European collaboration will need to be redefined when the Medicines & Healthcare products Regulatory Agency and the Veterinary Medicines Directorate most likely are withdrawing from the European collaboration after 1 April 2019.

I look forward to continuing our dialogue and the work we do together as I am convinced that close dialogue with all central stakeholders is essential for the Danish Medicines Agency to take the next big steps towards becoming one of Europe's best in class.

Thank you for your collaboration throughout 2017 – I look forward to continuing work in 2018!

Sincerely,

Thomas Senderovitz

Director General

Summary of product characteristics – read it right

It is important that doctors know what the individual sections of the summary of product characteristics (SmPC) say when they prescribe medicines. DR (the Danish Broadcasting Corporation) recently put focus on the SmPCs of opioids.

In December 2017, a DR broadcast *"Smerter til salg"* (literally: pain for sale) put focus on the Danes consumption of opioids, etc. It is a topic of current relevance since several thousands of Danes take strong painkillers on a daily basis. And given the American opioid crisis, it was obvious for DR to take a critical look at the situation at home.

The Danish Medicines Agency wants to make it absolutely clear that opioids should be prescribed cautiously – and no patients should be given medicine that gives them no benefits. For the same reason, we welcome that the Danish Health Authority, and especially the Institute for Rational Pharmacotherapy, which gives advice to general practitioners, have focus on precisely pain treatment in 2017 and 2018.

The DR broadcast featured the product Palexia Depot, which is authorised for adults with severe chronic that can only be managed adequately with opioids.

The SmPC contains several thorough warnings about the risk of dependence, and the medicine is subject to the tightest possible restrictions, implying among other things that what the doctors prescribe may be monitored.

The warnings appear from section 4.4 of the SmPC, the most essential section for doctors when they need to find out what special warnings and precautions of use apply to the use of a drug.

Below is a translation into English of section 4.4. of the Danish SmPC of Palexia Depot. Section 4.4 Special warnings and precautions for use. Risk of abuse and addiction/ Dependence Syndrome

Palexia Depot has a potential for abuse and addiction. This should be considered when prescribing or dispensing Palexia Depot in situations where there is concern about an increased risk of misuse, abuse, dependence, or resale.

All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and dependence.

The Danish SmPC of Palexia Depot thus describes very clearly that the drug may induce dependence.

The difference between section 4.4 and section 4.8
Even though the SmPC makes it very clear that Palexia Depot may induce dependence, the DR broadcast criticized the Danish Medicines Agency for having authorised the drug with a rare risk of dependence.

The point is that DR focused on the wording of the SmPC's section 4.8, which is a reproduction of the trials conducted with trial subjects prior to the medicine’s authorisation.

To understand the core nature of the problem, it is quite essential that you learn and understand how the different sections of an SmPC are made.

Whereas section 4.4 contains the general warnings related to the use of the drug, the frequency of adverse reactions in section 4.8 only reproduces the clinical trials that were conducted to test the drug prior to its approval.

It appears clearly that the SmPC's frequency calculations in section 4.8 have been made based on clinical trials and not on the medicine's use in "real life". It is only possible to calculate the frequency of adverse reactions based on a clinical trial because you know exactly how many participated and how many experienced adverse reactions. It is not possible to make the same frequency calculations when the medicine is used in the public.

It is well known that trial subjects are generally fitter, healthier and stronger than "real patients". "Real patients" often have far more complex medical histories, and many take several types of medicines concomitantly. Some may have abuse problems or other lifestyle factors affecting the effect of the medicine, all of which makes them unfit to participate in a clinical trial that seeks to obtain knowledge about the effect of the medicine seen in isolation.

The frequencies described in section 4.8 are based on the investigations that formed the basis for approval and which tested the specific medicine in a group of trial subjects. When a medicine has been on the market for some time, additional information may be added to the section about adverse reactions if new knowledge emerges after it was marketed.

Doctors must refer to the entire SmPC when prescribing medicines and must keep all precautions and warnings in mind when they assess each patient's risks of adverse reactions and dependence.

Palexia Depot is an opioid, and opioids may cause dependence. It is a well-documented class effect. For this reason, it is written clearly in section 4.4 of the SmPC that Palexia Depot may cause dependence, regardless of the fact that not all trial subjects experienced dependence.

Let's explain this more clearly with an example:

A company applies for authorisation of a new contraceptive pill. It is known and has been well-documented for many years that contraceptive pills prevent pregnancy but increase the risk of blood clots at the same time.

The company submits a number of clinical trials that meet all requirements for authorisation, but in the clinical trials testing the new contraceptive pill none of the participating trial subjects have blood clots.

*In section 4.8, which is a reproduction of the clinical trials, the company therefore cannot write anything about a frequency of blood clots based on the clinical trials – since there were no women in the trials who had blood clots. The frequencies described in section 4.8 are based **only** on the findings in the clinical trials.*

However, since there is solid evidence that contraceptive pills increase the risk of blood clots, it will naturally appear from section 4.4 of the SmPC which concerns special warnings and precautions of use.

The frequency of adverse reactions in clinical trials will for many medicines be described as more rare than experienced in "real patients", who are often more ill and have more complicated conditions than trial subjects in general.

I order to obtain the best possible knowledge about the efficacy of a medicine in "real patients", it is absolutely essential that the doctors who prescribe the medicine report adverse reactions to us. It must be done via the right channels, providing a proper and professional description of what the doctors have observed. Only doctors and patients can observe how the medicines work and are tolerated in long-term use – and it is therefore absolutely essential that we receive ADR reports that can give us the needed knowledge about medicines after people have started taking them.

Report adverse reactions to the Danish Medicines Agency at *www.meldenbivirkning.dk* (report a side effect).

Medicinal cannabis pilot programme from the new year

The act on the medicinal cannabis pilot programme was adopted Friday 15 December, and soon doctors may prescribe the first products.

The website of the Danish Medicines Agency has now been updated with information about the medicinal cannabis pilot programme for both healthcare professionals, companies and citizens, and we have held both a seminar and a press briefing about the pilot programme. However, as there is still a great need for information, we welcome you to submit comments, whether favourable or critical, to the information via our website.

Seminar on medicinal cannabis at the Danish Medicines Agency

On 18 December 2017, we announced that there are presently two cannabis products on the DKMA’s list of products admitted to the pilot programme. The products are:

Bedrocan CannGros
Product form: Herbal tea (dried, finely divided cannabis flower)
Strength: 220 mg/g THC (pack size 5 g)
Method of administration: Tea or possibly inhalation using a vaporizer

Bediol CannGros
Product form: Herbal tea (dried, granulated cannabis flower)
Strength: 63 mg/g THC + 80 mg/g CBD (pack size 5 g)
Method of administration: Tea or possibly inhalation using a vaporizer

The products may be prescribed from 1 January 2018.

Under the pilot programme, companies apply to have a specific cannabis product admitted to the pilot programme. The company must in parallel apply for an authorisation as a so-called intermediate product manufacturer – in practice an authorisation to import and repackage medicinal cannabis products for the pilot programme before the packages can be delivered to the pharmacies.

Presently eight companies have applied for authorisation as intermediate product manufacturers. CannGros is the first company to have obtained an authorisation and thus the first company to offer cannabis products in the pilot programme.

The range of cannabis products available in future will depend on what products the companies (intermediate product manufacturers) choose to import to Denmark. In the long term, it is intended that products cultivated in Denmark will also be included in the pilot programme.

The import product is called a cannabis primary product. A cannabis primary product is a product manufactured for medicinal use in another country. When the product has entered Denmark, it becomes a cannabis intermediate product by receiving a Danish label, a Danish product sheet, etc. When the product is finally prepared at the pharmacy for a certain patient, it is termed a cannabis product.

Where can doctors see the products available?
Doctors who wish to prescribe cannabis, can see the available products on the list of admitted cannabis intermediate products on the website of the Danish Medicines Agency.

The list of cannabis intermediate products shows which products are admitted to the pilot programme. Doctors looking for more detailed information about the individual products must refer to the product sheets of the individual products, also available on the website of the Danish Medicines Agency.

Doctors can find the products available for prescription in Medicine Prices, which lists the product price which is fixed for a period of 14 days – just like authorised prescription-only medicines.

Information about the cannabis products will also be available in the systems doctors use in their daily practice. The information available may vary between the systems used by the doctors. In principle, the information displayed should reflect the current information in Medicine Prices, and the doctor will be able to see the name, strength, pack size and route of administration of the cannabis product in question as well as the indications covered by

the Danish Medicines Agency's guidelines for doctors on the medicinal cannabis pilot programme.

There is no information about the pilot programme's cannabis products on Produktresume.dk or Promedicin.dk.

Guidelines for doctors
The guidelines for doctors on the treatment of patients with medicinal cannabis covered by the pilot programme are available at the DKMA website in Danish only: Vejledning om lægers behandling af patienter med medicinsk cannabis omfattet af forsøgsordningen

Since knowledge is insufficient in many areas, the guidelines cannot be considered to represent an actual treatment guide. The guidelines include no product-specific information on the cannabis products comprised by the pilot programme, but are based on existing knowledge about the effects and side effects of THCs and CBDs.

The guidelines list the indications that the Danish Medicines Agency believes may be relevant to treat with medicinal cannabis. In brief, it is our assessment that medicinal cannabis should be considered only for indications that are supported by evidence that medicinal cannabis may have an effect.

The relevant indications are:

- Painful spasms caused by multiple sclerosis
- Painful spasms caused by spinal cord damage
- Nausea after chemotherapy
- Neuropathic pain, i.e. pain due to a disease of the brain, spinal cord or nerves.

The Danish Medicines Agency has selected the indications after studying and assessing the relevant scientific studies conducted worldwide to investigate the effect of medicinal cannabis. The specific products comprised by the pilot programme have not necessarily been investigated. Nor have the possible adverse reactions in the short and long term been identified sufficiently, which is something doctors and patients must pay attention to and accept.

Doctors may prescribe the products of their choice, which means that all doctors may prescribe the products comprised by the pilot programme to their patients. Neither the law nor the pilot programme's guidelines prevent doctors from prescribing medicinal cannabis to patients with other illnesses than those appearing from the guidelines. It is important to stress, however, that no doctor has an obligation to prescribe medicinal cannabis.

Doctors are subject to stricter reporting requirements in the trial period
Throughout the medicinal cannabis trial period, doctors have an increased obligation to report adverse reactions. It means that doctors must report all suspected adverse reactions from medicinal cannabis to the Danish Medicines Agency.

A serious adverse reaction must be reported to the DKMA no later than 15 days after the doctor became aware of an adverse reaction.

Adverse reactions are reported to the Danish Medicines Agency on an electronic form available at meldenbivirkning.dk (report a side effect).

New products in the pilot programme
The intention is to include more products in the pilot programme along the way. A list of cannabis primary products included in the programme will also be available on the website of the Danish Medicines Agency.

The same cannabis primary product can be imported by more than one intermediary product manufacturer. This opens up to competition and substitution of these cannabis intermediate products.

The lists of cannabis intermediate products and cannabis primary products are updated regularly on the website here (in Danish only).

Cultivation of medicinal cannabis
Alongside the pilot programme a development scheme has been launched with the purpose of giving manufacturers based in Denmark an opportunity to develop cultivation methods for the manufacture of medicinal cannabis. This scheme will start at new year; as of 15 December, 11 authorisations had been granted to companies that applied for authorisation to cultivate cannabis.

The list of authorised applicants can be seen here (in Danish only)

Clarithromycin and cardiac events

The antibiotic medicine clarithromycin and the risk of sudden death have long been the subject of discussion. The European Pharmacovigilance Risk Assessment Committee, PRAC, has just completed a thorough review of studies and other literature on clarithromycin, concluding that there is not sufficient evidence that the medicine causes sudden death several years after treatment.

Researchers all over the world have for years been investigating if clarithromycin treatment increases the risk of serious cardiac events such as cardiac arrhythmia, myocardial infarction and sudden death. As a result, the literature available in the area is extensive, covering a long line of published clinical trials and epidemiological studies, including several registry studies and meta analyses.

Some studies have investigated the risk of cardiac events during treatment with clarithromycin or for a short period after cessation of clarithromycin (short-term effect); other studies have investigated the risk several years after cessation of treatment (long-term effect).

The studies investigating the short-term effect (Svanstrom et al., Wong et al, Root et al., Cheng et al.) show overall that there is a small increase in the risk of cardiac death and myocardial infarction, which is consistent with clarithromycin's and other so-called macrolides' capacity to affect heart rhythm. Clarithromycin may cause cardiac arrhythmia (QT prolongation) and in the worst case scenario the life-threatening heart rhythm condition torsade de pointes and sudden death. This information appears already in the product information of clarithromycin so that doctors can weigh the risk of adverse reactions against clarithromycin's beneficial effect on serious and potentially life-threatening infections.

The studies investigating the long-term effect produced contradictory results. The researchers behind the clinical trial CLARICOR (Jespersen et al.) and two observational studies (Schembri et al., Mosholder et al.) saw an association between clarithromycin and cardiac events from 1 and up to 10 years after clarithromycin treatment was stopped – primarily in people with existing cardiovascular disease (ischaemic heart disease) and who were not treated with statins. Other studies (Andersen et al., Root et al., Wong et al.) did not find such an association. All studies suffer from significant methodological weaknesses.

Unlike the long-term effect, which is well-explained, it has not been possible to find a mechanism that may explain why short-term treatment with clarithromycin should increase the risk of cardiac death many years later. A newly published Danish study (Larsen et al.) suggests that clarithromycin increases oxidative stress – i.e. oxidation in the body. Further studies are needed to clarify if there is an association between increased oxidation and cardiac events.

PRAC emphasises that the observed risks should be weighed against clarithromycin's important place in the treatment of serious and life-threatening infections. Based on the overall knowledge, PRAC recommends the following changes to the product information of clarithromycin-containing medicines:

Heading will be changed from "Prolongation of QT interval" to "Cardiovascular events": "Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin."

List of the literature reviewed by PRAC and the basis of its conclusion:

Andersen SS, Hansen ML, Norgaard ML, et al. Clarithromycin use and risk of death in patients with ischemic heart disease. Cardiology. 2010; 116(2):89–97.

Andraws R, Berger JS, Brown DL. Effects of antibiotic therapy on outcomes of patients with coronary artery disease: a meta-analysis of randomized controlled trials. JAMA. 2005; 293(21):2641–7.

Berg HF, Maraha B, Scheffer GJ, et al. Treatment with clarithromycin prior to coronary artery bypass graft surgery does not prevent subsequent cardiac events. Clin Infect Dis. 2005; 40(3):358–65.

Berni E, de Voogd H, Halcox JP, et al. Risk of cardiovascular events, arrhythmia and all-cause mortality associated with clarithromycin versus alternative antibiotics prescribed for respiratory tract infections: a retrospective cohort study. BMJ Open. 2017;7(1):e013398

Cheng YJ, Nie XY, Chen XM, et al. The role of macrolide antibiotics in increasing cardiovascular risk. J Am Coll Cardiol. 2015; 66(20):2173–84.

Chou HW, Wang JL, Chang CH, et al. Risks of cardiac arrhythmia and mortality among patients using new-generation macrolides, fluoroquinolones, and beta-lactam/beta-lactamase inhibitors: a Taiwanese nationwide study. Clin Infect Dis. 2015; 60(4):566–77.

Giamarellos-Bourboulis EJ1, Mylona V, Antonopoulou A, et al. Effect of clarithromycin in patients with suspected Gram-negative sepsis: results of a randomized controlled trial. J Antimicrob Chemother. 2014 Apr;69(4):1111-8.

Gluud C, Als-Nielsen B, Damgaard M, et al. Clarithromycin for 2 weeks for stable coronary heart disease: 6-year follow-up of the CLARICOR randomized trial and updated meta-analysis of antibiotics for coronary heart disease. Cardiology. 2008;111(4):280–7.

Jensen GB, Hilden J, Als-Nielsen B, et al. Statin treatment prevents increased cardiovascular and all-cause mortality associated with clarithromycin in patients with stable coronary heart disease. J Cardiovasc Pharmacol. 2010;55(2):123–8.

Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. BMJ. 2006; 332(7532):22–7

Jespersen CM, Kolmos HJ, Frydendall N, et al. Compliance with and short-term adverse events from clarithromycin versus placebo in patients with stable coronary heart disease: the CLARICOR trial. J Antimicrob Chemother. 2009; 64 (2): 411-5

Larsen EL, Cejvanovic V, Kjær LK et al. Clarithromycin, trimethoprim and penicillin and oxidative nucleic acid modifications in humans: randomized controlled trials. Br J Clin Pharmacol. 2017

https://www.ncbi.nlm.nih.gov/pubmed/?term=Mosholder%20AD[Author]&cauthor=true&cauthor_uid=29036565Mosholder AD, Lee JY, Zhou EH, et al. Long-term risk of acute myocardial infarction, stroke and death with outpatient use of clarithromycin: a retrospective cohort study.Am J Epidemiol. 2017 Sep 20.

Root AA, Wong AY, Ghebremichael-Weldeselassie Y, et al. Evaluation of the risk of cardiovascular events with clarithromycin using both propensity score and self-controlled study designs. Br J Clin Pharmacol. 2016; 82(2):512–21.

Schembri S, Williamson PA, Short PM, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. BMJ. 2013;346:f1235

Sinisalo J, Mattila K, Valtonen V, et al. Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-q-wave coronary syndrome. Circulation. 2002; 105(13):1555–60.

Sligl WI, Asadi L, Eurich DT, et al. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. Crit Care Med. 2014 Feb; 42(2):420-32.

Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. BMJ. 2014;349:g4930.

Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ. 2016;188(7):E120–9.

Winkel P, Hilden J, Fischer Hansen J, et al. Excess sudden cardiac deaths after short-term clarithromycin administration in the CLARICOR trial: why is this so, and why are statins protective? Cardiology. 2011; 118(1):63–7

Winkel P, Hilden J, Hansen JF, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10 years in the CLARICOR randomised, blinded clinical trial. Int J Cardiol. 2015;182: 459–65.

Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016;352:h6926.

Wong AYS, Chan EW, Anand S, et al. Managing Cardiovascular Risk of Macrolides: Systematic Review and Meta-Analysis. Drug Saf. 2017 Aug;40(8):663-677. doi: 10.1007/s40264-017-0533-2.

Two new studies on the use of contraceptive pills and adverse reactions

Two new studies on contraceptive pills were published in the beginning of December – one studying an association between the use of homonal contraception and suicidal behaviour in women, *Association of Hormonal Contraception With Suicide Attempts and Suicides, Skovlund et al*., and one studying the association between breast cancer and the use of hormonal contraception (significant for women above the age of 40), *Contemporary Hormonal Contraception and the Risk of Breast Cancer.*

The Danish Medicines Agency has reviewed the two studies and forwarded both signals in the European system.

Association of Hormonal Contraception With Suicide Attempts and Suicides, Skovlund et al.
According to the authors, it is the first time that a possible association between hormonal contraception and suicidal behaviour (suicide attempts and suicides) is studied specifically. A number of previous studies have investigated an association between the use of contraceptive pills and the risk of death in general – including especially cardiovascular- and cancer-related death and in certain studies also violent and accidental deaths, such as suicide. But contrary to this new study, the different hormonal contraceptives were not analysed separately, and the temporal associations have not previously been analysed in detail.

The study Association of Hormonal Contraception With Suicide Attempts and Suicides, Skovlund et al. distinguishes itself from earlier studies by being a registry-based study enrolling 475,802 women from age 15 and upwards, with no prior use of hormonal contraception, who were monitored in the period 1996-2013. During the trial period 54 per cent of the women started using some form of hormonal contraception. A total of 6,999 first suicide attempts and 71 suicides were identified among all women.

In the study population of women who start hormonal contraception there were twice as many suicide attempts and three times as many suicides compared to women of the same age not using hormonal contraception. The increased risk of suicide attempts is highest among the 15 to 19-year-olds. The risk of suicidal behaviour was highest shortly after the commencement of hormonal contraception, a tendency which was observed across the different types of hormonal contraceptives (i.e. various types of contraceptive pills, hormone-releasing intrauterine devices and subcutaneous implants, etc.) with different hormone concentrations.

The study appears to be well-designed and well-conducted with the focus on an association between hormonal contraceptive use and suicidal behaviour. Significant factors have been taken into account such as temporal association and psychosocial factors. In addition, a number of analysis have been completed, e.g. of the significance of start of sexual activity and predisposition to depression in the family.

The authors encourage greater awareness of the risk of mood swings when patients start taking hormonal contraceptives.

The product information of the various types of hormonal contraceptives describes depression, sadness, mood swings or depressed mood are described as adverse reactions, but not suicidal behaviour.

We have now chosen to raise suicidal behaviour as a possible ADR signal in the EMA.

Contemporary Hormonal Contraception and the Risk of Breast Cancer, Lidegaard et al. A higher risk of breast cancer in women using hormonal contraception is a well-known problem. It appears from the product information of hormonal contraceptives that breast cancer is a known adverse reaction/possible risk (a small increase in risk).

In the new study, a higher risk was seen for the various types of hormonal contraceptives. The study specifically shows that women who use hormonal contraceptives are exposed to an approximately 20% higher risk of breast cancer – the most common form of cancer among women. The risk is at the same level as that seen for contraceptive pills used years ago. The risk increases with age, which means the study results are primarily relevant for women in their 40s. The study has analysed the different types of hormonal contraceptives separately, including the different generations of contraceptive pills. The influence of the length of treatment and any previous use of hormonal contraceptives were analysed as well. The increased risk of breast cancer can apparently be seen several years after cessation of hormonal contraception, especially among the slightly older women whose risk is highest because of the already significantly higher risk of breast cancer.

Since the study submits new information about the risk of breast cancer independently from the various types of hormonal contraceptives, the Danish Medicines Agency will also be raising this issue as an ADR signal in the EMA.

Not until the studies have been reviewed and assessed at the European level will we know if it will affect the assessment of the medicines' safety and future recommendations on the use of hormonal contraception.

New study on hydrochlorothiazide and the risk of skin cancer

In the beginning of December, a new Danish study caused something of a stir in most Danish media. The study *A nationwide case-control study from Denmark* showed an association between hydrochlorothiazide, a frequently used antihypertensive and diuretic drug, and squamous cell carcinoma.

The high level of attention led several doctors and patients to contact the Danish Medicines Agency and the Danish Health Authority to hear how it will impact treatment and the drug. Both authorities have stated that the study should not make people stop their treatment with hydrochlorothiazide without consulting their doctor first. No conclusions should be drawn before the risk has been assessed at EU level.

Several prior studies have also investigated the risk associated with diuretics and antihypertensives, but this new study is special because the researchers have measured

the total consumption of the different antihypertensive and diuretic substances – including hydrochlorothiazide – in a well-designed registry-based study. The researchers looked back and demonstrated that people with squamous cell carcinoma had used hydrochlorothiazide far more frequently than people without skin cancer. The concrete findings of the study is that long-term use of hydrochlorothiazide increases the risk of developing squamous cell carcinoma by up to seven times. The increased risk was not observed for other diuretic og antihypertensive substances.

Increased photosensitivity is a well-known adverse reaction of hydrochlorothiazide, and it is well-known that too much exposure to the sun increases the risk of skin cancer – especially among people with fair skin. The risk of developing squamous cell carcinoma is generally low. According to the study, it is primarily people who have taken the drug for many years who have an increased risk of squamous cell carcinoma.

The results of the study should be weighed against the other knowledge in the area before final conclusions can be drawn. After the study was published, the Danish Medicines Agency raised this possible adverse reaction of hydrochlorothiazide as a signal in the EMA in order to obtain an overall European assessment of the conclusions that can be drawn and what precautions to take.

Hydrochlorothiazide is a sub-component in several antihypertensive drugs and in potassium-sparing diuretics and is rarely used as a diuretic alone. The common treatment of squamous cell carcinoma is surgery, and there is only a small risk of spread of this type of cancer form. The study found no association between other antihypertensive or diuretic drugs and skin cancer.

Please also see the Danish Medicines Agency's announcement: DKMA comments on the new hydrochlorothiazide study (in Danish only)

The Danish Health Authority's announcement: Hydrochlorothiazide linked to skin cancer (in Danish only).

Prolonged-release paracetamol withdrawn from the market

The European Medicines Agency has confirmed its previous recommendation to withdraw modified- or prolonged-release paracetamol products from the market. The withdrawal takes place because of difficulties of managing overdose after ingestion – when used correctly prolonged-released paracetamol is safe. Immediate-release paracetamol is not affected and will continue to be available as before.

In September 2017, the European Pharmacovigilance Risk Assessment Committee, PRAC, decided based on a review of prolonged-release paracetamol that it should be withdrawn from the market. Two pharmaceutical companies that market modified-release

paracetamol and modified-release paracetamol in combination with tramadol subsequently requested a re-examination of the medicines.

In its assessment of prolonged-release paracetamol, PRAC consulted specialists within pain treatment and intoxication and other experts. The PRAC confirmed its previous conclusion that the advantages of having longer-acting products on the market do not outweigh the disadvantages of managing an overdose of these medicines. The reason is that the usual way of treating an overdose of immediate-release paracetamol is not appropriate for modified-release tablets. In many cases, it is uncertain if an overdose was caused by immediate-release or modified-release paracetamol, which is important to know to identify the treatment needed to reduce the risk of severe liver injury or death.

The withdrawal is expected to take effect within a few months and applies to the following products:

- Pinex Retard
- Panodil modified-release tablets
- Panodil Retard.

Doctors may in special cases apply to the Danish Medicines Agency for a compassionate use permit for the dispensing of prolonged-release paracetamol for individual patients.

We advise patients who have questions about their medicine to consult their own doctor.

Marketing authorisation for certain gadolinium-containing contrast agents is suspended

The marketing authorisations of a number of gadolinium-containing contrast agents for MRI scans will be suspended, and the use of certain other contrast agents will be restricted. This is the conclusion after a review by the EMA with Denmark as one of the leading forces.

Recent studies have shown that the chemical element gadolinium may accumulate in the brain tissue in patients undergoing MRI scans using gadolinium-containing contrast agents. In the spring of 2016, the European Pharmacovigilance Risk Assessment Committee therefore initiated a review and assessment of the risk of accumulation of gadolinium in the brain tissue after MRI scans. The final conclusion came in November 2017.

The table below shows which gadolinium-containing contrast agents will be suspended, which will be subject to limited authorisation, and which will maintain their authorisation unchanged.

Overview of the EMA's recommendations on gadolinium-containing contrast agents authorised in the EU and in Denmark.

Product	Type (formulation)	Authorisation status EU	Authorisation status DK
Artirem/Dotarem/ Dotarem Arthro (gadoteric acid)	Macrocyclic (intra-articular)	Maintained	Maintained
Dotarem (gadoteric acid)	Macrocyclic (i.v.)	Maintained*	Maintained (Dotarem and Dotagraf)
Gadovist (gadobutrol)	Macrocyclic (i.v.)	Maintained	Maintained
Magnevist (gadopentetic acid)	Linear (intra-articular)	Maintained	Maintained
Magnevist (gadopentetic acid)	Linear (i.v.)	Suspended**	Dereg. in 2016
MultiHance (gadobenic acid)	Linear (i.v.)	Restricted to liver scans	Restricted to liver scans
Omniscan (gadodiamide)	Linear (i.v.)	Suspended	Deregistered in 2015
Optimark (gadoversetamide)	Linear (i.v.)	Suspended	Deregistered in July 2017
Primovist (gadoxetic acid)	Linear (i.v.)	Maintained (registered only for use in liver scans)	Not authorised
ProHance (gadoteridol)	Macrocyclic (i.v.)	Maintained	Maintained

* Plus the generic products: Cyclolux, Dotagita, Dotagraf, Dotamulti, Dotaspin, DotaVision, Gadoteerzuur Guerbet Gadotersäure Sanochemia.

** Plus the generic products: Gadocon, Gadolan, Gadopent, Gadopentat, Gadopur, Gadothek, Magnegita, Magnetolux, Magnevision, Magnograf, MR-Lux.

The marketing authorisation for the intra-articular formulation of gadopentetic acid is maintained since the dose of gadolinium used for joint injections is very low and since the patients often do not need repeated injections.

All the macrocyclic contrast agents that have been examined (gadobutrol, gadoteric acid and gadoteridol) will still be authorised for their current indications.

Note for health professionals
Because the use of all gadolinium-containing contrast agents may cause gadolinium accumulation, doctors and healthcare professionals are recommended to use gadolinium contrast agents only when essential diagnostic information cannot be obtained otherwise, using the lowest dose that provides sufficient enhancement for diagnosis. The product information of gadolinium contrast agents will be updated with this information.

The result of EMA's assessment
In its review of gadolinium agents, the EMA found convincing evidence of accumulation of gadolinium in the brain, partly in studies directly measuring gadolinium in brain tissues, and partly in studies showing increased signal intensity on MRI scans of the brain many months after the last injection of a gadolinium contrast agent. Whereas macrocyclic contrast agents disappear quickly from the brain, the linear contrast agents remain in the brain for up to 12 months or more.

Although, there have so far been no reports of clinical adverse reactions in relation to accumulation of gadolinium in the brain, it is recommended to suspend the marketing authorisation as a precautionary measure.

Deposition of gadolinium in other organs and tissues has been associated with rare adverse reactions such as skin plaques and nephrogenic systemic fibrosis. These adverse reactions could have serious consequences for patients with reduced renal impairment, which is why the agents are contraindicated in the product information in these patients. Animal studies have furthermore shown that gadolinium is toxic and harmful in tissues.

Gadolinium contrast agents are diagnostic products given to patients before or during MRI scans to obtain better images of organs and tissues. After administration, the gadolinium chelate is mostly eliminated via the kidneys. However, gadolinium can accumulate in some organs, such as in the liver, kidneys, muscles, skin and bones, and lately evidence of accumulation in the brain has also been found.

Gadolinium contrast agents are categorised depending on the structure of the chelate in linear and macrocyclic agents. Linear agents have a structure more likely to release gadolinium from the chelate molecule, which means it can accumulate in body tissues. Macrocyclic gadolinium contrast agents are more stable and thus release gadolinium to a much lower degree.

Relevant doctors and healthcare professionals have received this information in a circulated DHPC. The letter is also available on the Danish Medicines Agency’s website here (in Danish only).

Read the press release of the EMA: EMA’s final opinion confirms restrictions on use of linear gadolinium agents in body scans.

Examination of the prostate cancer drug Xofigo initiated by EMA

The first data from a clinical study of Xofigo have shown an increased risk of death and fractures when used in combination with the cancer medicine Zytiga and the corticosteroid prednison/prednisolone. The European Medicines Agency has initiated a review of the medicine as a result.

The clinical trial has compared Xofigo with placebo – both given in combination with Zytiga (abiraterone acetate) and prednison/prednisolone. The study includes patients with prostate cancer both with and without symptoms, such as pain.

A preliminary analysis shows a frequency of death of 27 per cent (109 of 401 patients) for the Xofigo combination compared to 20 per cent (82 of 405 patients) for the placebo combination. Fractures also occurred more frequently with use of the Xofigo combination compared with use of the placebo combination (24% versus 7%).

The patients included in the study have stopped treatment with Xofigo and are monitored closely.

The EMA will review the results of the study together with other available data to evaluate if the results will impact the use of Xofigo.

Note for doctors
While the review is ongoing, doctors are advised not to use Xofigo in combination with Zytiga and prednison/prednisolin to treat metastatic castration-resistant prostate cancer.

We advise patients who take Xofigo to consult their doctor if they have questions about their treatment.

Relevant doctors and other healthcare professionals have received this information in a circulated DHPC. The letter is available on the website of the Danish Medicines Agency here.

About Xofigo

Xofigo is used for the treatment of men with prostate cancer. Xofigo is authorised for treatment in cases of castration-resistant prostate cancer when the disease has spread to the bone but is not known to have spread to other internal organs and is causing symptoms such as pain.

Read the press release of the EMA here.

When pharmaceutical companies in third countries fail to comply with GMP

Recently, the specialised press has brought several stories about pharmaceutical companies in third countries not meeting the requirements for good manufacturing practice – the so-called GMP rules that apply to the manufacture of medicines. A few cases may concern fraudulent manufacturing, but this is not the normal picture.

It is absolutely essential for the quality of medicines that they are manufactured according to the stringent EU rules that apply to good manufacturing practice. It is equally essential that we can trust the data based on which medicines are approved and marketing authorisations are granted. In our role as drug regulatory authority in Denmark, we routinely inspect the Danish companies that handle medicines, including those that for example manufacture active substances in drugs or carry out clinical trials, etc. When we inspect the companies that manufacture medicines, we look at whether they meet the GMP rules. When we have verified through an inspection that a company meets the GMP rules, we issue a GMP certificate, which is publicly available in the European EudraGMDP database.

Danish companies can also choose to buy active pharmaceutical ingredients manufactured in countries outside the EU or to have a medicine manufactured in part or in whole in a third country. If they do, special requirements apply – not only for the control of the company in the third country, but also for analysis and release of the products from that country. The pharmaceutical company in Denmark must ensure through regular inspections (so-called audits) that GMP is complied with by the company in the third country. The drug regulatory authorities in the EU also regularly inspect the companies in the third countries that supply medicines to companies on the European market; Denmark participates here as well, e.g. in India, China and other third countries to inspect companies on behalf of the EU. Companies in third countries meeting the GMP rules are also granted a GMP certificate.

If an inspection reveals that a company fails to comply with GMP in serious areas, the EU drug regulatory authority handling the inspection will issue a statement of non-compliance with GMP. Such a statement usually has far-reaching implications, but it depends on what kind of major deficiencies are identified. If, for example, there is a risk that the medicine has not been manufactured according to GMP, the Danish pharmaceutical company will often have to recall the medicine from the market, or the Danish company will have to find another supplier.

The statement of non-compliance with GMP is issued regardless of whether it concerns fraudulent activities, the lack of competencies in the company or the like in the manufacturing company, but the consequences may be different. Cases about non-GMP compliance are typically coordinated between the European Medicines Agency (EMA), the inspectors who inspected the company in question in the third country and representatives from the EU countries that have affected products on their markets. This ensures quick and coordinated measures that may be adapted to the individual EU country’s terms and needs.

If the company remedies its major deficiencies to become GMP compliant once again, it may be granted a new GMP certificate after a new inspection has verified that it meets the requirements.

Where irregularities in clinical trials are concerned, the outcome could be that the marketing authorisations are withdrawn together with the medicines on the market.

Antibiotic recalled due to increased levels of histamine

– how the reporting of adverse reactions may improve medicines safety

Reports of anaphylactic reactions in horses after injection of the antibiotic gentamicin triggered a major investigation of the medicine's safety. The result showed increased levels of histamine in gentamicin raw material. The Danish Medicines Agency has together with other authorities, Danish hospitals and companies responded to ensure that patients can still be treated safely with gentamicin.

In 2015 and 2016, veterinarians across the EU reported increased cases of anaphylactic reactions in horses after injection of the antibiotic gentamicin. It raised suspicion among European drug regulatory authorities that there might be a problem with the quality.

The Danish Medicines Agency received no reports of reactions in horses in Denmark, but we were made aware of the observation through our collaboration with the other drug regulatory authorities in the EU through the exchange of information about product defects and suspected adverse reactions, etc. The suspicion prompted the manufacturer of the active substance gentamicin to investigate the possible causes.

In December 2016, we received five ADR reports of blood pressure drops in human beings treated intravenously with gentamicin to prevent infection in connection with surgical procedures. The ADR reports entered a so-called signal in the Danish Medicines Agency's pharmacovigilance system. The blood pressure drops were of a short duration and were not serious, so we decided to await the results of the gentamicin investigation initiated by the manufacturer.

Company manufacturing gentamicin raw material finds increased levels of histamine
During 2017, the manufacturer of gentamicin raw material established that increased levels of histamine were contained in the gentamicin raw material manufactured in a certain period. Histamine is normally present in gentamicin in very small quantities, but for a period of time the content was significantly higher. This was due to one of the ingredients used to manufacture gentamicin raw material. No one had previously been aware that histamine in gentamicin raw material could be problematic, and so far, no systematic tests have been conducted to establish the quantity of histamine in this raw material.

It is likely that the reactions observed in human beings and horses were due to increased levels of histamine in the gentamicin products. Since no specific analytical method for histamine had been developed, it was not possible to investigate directly if certain medicines posed a risk to patients. We therefore sent out information to healthcare staff in the hospitals, advising them to pay attention to the likelihood of increased levels of histamine in gentamicin products for injection, and that patients should therefore be monitored after injection due to the risk of reactions like drops in blood pressure. We also encouraged the reporting of any adverse reactions after injection of gentamicin. Our focus was also on veterinary gentamicin products. We assessed that there were no similar problems for the products in Denmark, which was supported by the fact that we had received no ADR reports about reactions in animals receiving gentamicin.

Information that increased levels of histamine had been found triggers inflow of ADR reports in Denmark

The information that we circulated triggered the submission of a number of ADR reports on blood pressure drops and other reactions consistent with the theory of increased levels of histamine in gentamicin. The ADR reports came mainly from the ADR manager attached to the hospitals in the North Denmark Region. We contacted other drug regulatory authorities in the EU to hear if they had experienced something similar. Their response showed a different pattern than that in Denmark, since gentamicin in many of the ADR reports had been co-administered with other types of antibiotics and anaesthetics. Also, most of the reactions occurring abroad seemed more consistent with anaphylaxis, which was not the case for those occurring in Denmark. Thus, nothing indicated that this was a problem affecting several places in the EU.

Gentamicin with increased levels of histamine recalled

In November 2017, we recalled gentamicin products for injection or infusion manufactured with gentamicin raw material with histamine levels above the threshold of 16 ppm (parts per million) in Denmark. We did so as a precautionary measure, and because a recall would no longer lead to shortage of the product. At the European level, a threshold value for histamine of 16 ppm for new batches was also set. Work was also initiated to prevent future problems of increased levels of histamine in gentamicin. At the same time, we contacted the regional medicinal products committees, asking them to inform doctors about the risk and the recall.

The most recent ADR report about gentamicin was received in October 2017. From now, any potential problems with the medicine will be monitored via the usual monitoring systems for adverse reactions and quality issues.

This case illustrates how the reporting of adverse reactions and the European and international collaboration are important to detect and solve potential problems with medicines.

Gentamicin is an antibiotic in the group of aminoglycosides for both human and veterinary use. The injection or infusion forms are used to treat serious infections such as sepsis or to prevent infections, e.g. in connection with surgical procedures. It is mostly co-administered with other types of antibiotics. Gentamicin has been used since the 1970s.

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Short news

Great turnout at the Danish Medicines Agency's information meetings about new medical devices regulations

In October and November, the Danish Medicines Agency invited stakeholders to two information meetings about medical devices to introduce them well to the two new regulations that enter into force in the area in 2020 and give the participants the opportunity to ask questions and discuss the matter. Both meetings were attended by some 120 stakeholders – including manufacturers, importers and distributors of medical devices.

Information meeting about the new medical devices regulations at the Danish Medicines Agency

The Danish Medicines Agency opened the meetings by presenting the main points of the new legislation. The medical devices industry then presented their perspectives on the new regulations. The participants could then engage in more detailed discussions of selected themes in cafe sessions.

The regulations are to strengthen patient safety and ensure the availability of new and innovative devices, which will be of benefit to patients. The regulations will impose new requirements on both the industry and the national authorities. It is therefore essential for the Danish Medicines Agency to maintain close dialogue and communication with manufacturers and the rest of the industry in the area.

The Danish Medicines Agency has afterwards received very positive feedback on the meetings.

Read more about the two regulations here: New medical devices regulations.

OTC medicines in the self-selection area

From 1 January 2018, a number of OTC medicines will be made available to consumers as self-selection products. In other words, the medicines will be placed in appropriately displayed self-selection areas of retail shops and not behind the counter.

Effective in the new year, the new rules about OTC medicines for self-selection come from a wish to promote the citizens' availability of medicines so they can select the OTC medicines themselves. It is also expected that the greater availability will enhance compliance – meaning that citizens will get the medicine they need according to the doctor's recommendations.

Medicines for self-selection and exemptions
Prior to the new arrangement, the Ministry of Health requested the DKMA to review the range of OTC medicines to assess which medicines would be suitable for inclusion in the self-selection system and which medicines would not. The following criteria were used to determine the product range:

- Medicines with expected improved effect/compliance based on improved accessibility
- Medicines that could lead to unnecessary increased consumption

The DKMA's assessment was presented to the Medicinal Products Committee and submitted for consultation among relevant stakeholders and posted on our website.

As of 1 January 2018, all OTC medicines in dispensing groups **HA** and **HF** may be placed in the self-selection area because pharmacists can advise consumers on the use of medicines at purchase.

Certain OTC medicines in dispensing group **HF** will *not* be available for self-selection in retail outlets because consumers cannot be offered advice on the use of medicines at purchase. Medicinal products in dispensing groups **HA18, HX** and **HX18** are not available for self-selection neither in pharmacies nor other retail shops.

List of all authorised medicinal products in dispensing group HF

By 1 January 2018, this list will include a column to indicate if a given HF medicine may be sold in the self-selection area in retail shops or not. Whereas the list of authorised HF medicines is updated daily, the column with details about self-selection is only updated every other week when new medicinal prices are published.

Since all medicines in dispensing groups HA and HF can be placed in the self-selection area at the pharmacy, there will be no list for pharmacies.

Medicines not available for self-selection

Follow-up after two years
After a period of two years, the Danish Medicines Agency will look at sales figures for all medicinal products available for self-selection to identify any inappropriate increases in the sale and use of certain types of medicinal products available for self-selection. In the affirmative, the DKMA will assess if the medicine in question should no longer be available for self-selection.

More information about the new rules is available at www.retsinformation.dk (in Danish only).

New rules for the issuance of prescriptions

Prescriptions and dose dispensed-medicines must now be submitted electronically as a general rule. This appears from a new executive order on prescriptions and dose dispensing, which entered into force on 1 October 2017.

It is expected that electronic submission as the primary way of prescribing medicines and dose dispensed medicines will increase assurance that correct data are transferred and reduce the possibilities of forging prescriptions.

The executive order includes changed rules for the issuance of prescriptions. The most important changes appear below.

Prescriptions for the following types of medicines must only be submitted electronically by doctors:

- Medicines for dose dispensing,
- Medicines subject to stricter monitoring, cf. section 4 of the executive order,
- Medicines for use in practice.

Paper, telefax and telephone prescriptions can still be used in special circumstances:

- When the doctor issues a prescription, he or she must assess if special circumstances prevail.
- There is no list of situations that may justify the use of paper, telefax and telephone prescriptions.
- Pharmacies must only execute paper, telefax and telephone prescriptions once. In repeat prescriptions, an electronic prescription must be used.
- It is not possible to use paper, telefax and telephone prescriptions for dos-dispensed medicines, medicines subject to stricter monitoring, cf. section 4 of the executive order, and medicines for use in practice.

From 1 April 2018, it will also be possible to use electronic prescriptions for magistral medicinal products.

Veterinarians' issuance of medicines

- Veterinarians can still issue medicines on paper prescriptions and use telephone and telefax prescriptions.
- Veterinarians who wish to issue medicines by email must use the PDF format via a secure, encrypted connection.
- Veterinarians must remember to write their civil registration number (CPR no.) on prescriptions for medicines subject to special monitoring, cf. section 4 of the executive order.

The executive order is available in Danish at Retsinformation: Executive order no. 1108 of 27 September 2017.

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:

- **Fingolimod (Gilenya)**: Contraindications in patients with cardiac conditions. Sent out 3 November 2017.
- **Eluxadolin (Truberzi)**: Risk of pancreatitis and sphincter of Oddi spasm. Sent out: 9 November 2017.
- **Midazolam (Buccolam)**: Announcement about potential product defect affecting Buccolam (midazolam) prefilled plastic syringes. Sent out 23 November 2017.
- **Daclizumab (Zinbryta)**: Restrictions on use due to the risk of fulminant liver failure. Sent out November 2017.
- **Misoprostol (Misodel vaginal insert)**: Reports of severe cases of uterine tachysystole not responding to tocolytic treatment. Sent out 24 November 2017.
- **Haloperidol and haloperidol decanoate (Serenase and Serenase Dekanoat)**: Serenase and Serenase Dekanoat, all dosage forms (tablets, oral solution, solution for injection). Sent out 27 November 2017.
- **Cladribine (Litak, Leustatin)**: Risk of Progressive multifocal leukoencephalopathy (PML). Sent out 1 December 2017.
- **Saccharomyces boulardii (Precosa 250 mg capsules, hard, and Precosa 250 mg powder for oral suspension, single-dose sachet)**: New contraindication for Saccharomyces boulardii in critically ill or immunocompromised patients. The product is not marketed in Denmark. The letter has not been sent out, but can be found on the Danish Medicines Agency's website.
- **Gadolinium-containing contrast agents:** Updated recommendations after the investigation of gadolinium retention in brain and other tissue.

The DHPCs are available at the DKMA website – most of them in Danish only: Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.