Danish Pharmacovigilance Update
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# The Danish Health and Medicines Authority encourages doctors to be aware of suspected long-term adverse reactions from the use of SSRIs in children and adolescents

Within a very short period of time, the Authority has received two adverse reaction reports concerning significant growth reduction in two children following initiation of treatment with the SSRI product sertraline. One of the children commenced treatment in 2011 and experienced growth reduction within the same year. The other child received treatment for two years prior to growth examination. The children followed their respective growth curve prior to initiating treatment.

The Danish Health and Medicines Authority's adverse reaction database contains a total of three reports of growth inhibition in children/adolescents from the use of an SSRI product. In Denmark, 5,266 children and adolescents aged 7-17 years have redeemed at least one prescription for an SSRI product during 2011. Half of them redeemed a prescription for sertraline (2,661).

## Fluoxetine and sertraline

In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine. It was not established whether the final adult height of these children will be affected, and the possibility of a delay in puberty could not be ruled out.

For sertraline, there is a lack of long-term data on safety in children and adolescents with respect to growth, maturation and cognitive and behavioural development.

## As a doctor you should be aware of the following:

- Growth and pubertal development (height, weight and Tanner stage) should be monitored during and after treatment with fluoxetine or sertraline. In case of growth inhibition, referral to a paediatrician should be considered.
- Cognitive and behavioural development should be monitored during long-term treatment.
- You should focus on the suspected long-term adverse reactions and report them to the Authority's adverse reaction database.

## Lack of data in the national health registers

Growth inhibition in children and adolescents could be recorded in the Danish National Patient Registry under the code for growth retardation. However, a data run carried out by the Statens Serum Institut, National Institute for Health Data and Disease Control, for the Authority shows that the recording of growth inhibition from the use of SSRIs is very limited and that it is not possible to monitor the development based on data under the above-mentioned code from the national health registers. Therefore, doctors are encouraged to report suspected adverse reactions from the use of SSRI products in children and adolescents that may contribute to the knowledge of long-term adverse reactions.

You can report suspected adverse reactions here *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*

You can find summaries of product characteristics for fluoxetine and sertraline at *www.produktresume.dk* (in Danish only).

You can find more information in the guidelines on medicinal treatment of children and adolescents with mental disorders on our website *Vejledning om medikamentel behandling af børn og unge med psykiske lidelser* (in Danish only).

### Indication for drugs containing sertraline and fluoxetine

Indication for sertraline: Children and adolescents with obsessive-compulsive disorder (OCD).

Indication for fluoxetine: Major depressive episodes, where the depression has not improved after 4-6 talk therapy sessions.

All cases referred to in the article originate from the Danish Health and Medicines Authority's adverse reaction database. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

## New recommendations for spray application of the tissue adhesive Evicel®

The European Medicines Agency's Committee for Medicinal Products for Human Use, CHMP, has completed a review of the benefits and risks associated with the fibrin sealants Evicel® and Quixil® that are approved for spray application with a gas device. The review was initiated based on a worldwide total of five reports of air embolisms (among them two fatal cases) since 2008 in association with the administration of Evicel®. All cases were related to the use of the spray device at higher-than-recommended pressures and/or in closer-than-recommended proximity to the tissue surface. Therefore, the CHMP recommends the below measures for the use of fibrin sealants in order to minimise the risk of air or gas embolisms.

### As a doctor you should be aware of the following:

- Evicel® should be sprayed using pressurised $CO_2$ only, instead of pressurised air, because the greater solubility of $CO_2$ in blood reduces the risk of embolisms.
- Evicel® should not be sprayed in endoscopic surgery.
- During open surgery: When applying sprayable Evicel® using a pressure regulator device, the maximum pressure should be 1.7 bar. The product should be sprayed at least 10 cm from the tissue surface.
- During laparoscopic surgery: Evicel® should only be sprayed if the spray distance recommended by the manufacturer can be accurately judged. The maximum pressure should be 1.4 bar, and the product should be sprayed at least 4 cm from the tissue surface.
- Prior to applying Evicel®, the surface area of the wound should be dried using standard techniques (e.g., intermittent application of compresses, swabs and use of suction devices).
- Blood pressure, pulse rate, oxygen saturation and end-tidal $CO_2$ should be closely monitored when spraying Evicel®, because of the possibility of air or gas embolism.

### Letter to treating doctors and update of summaries of product characteristics

A letter will be sent to doctors treating with Evicel® to inform them about the new recommendations. The summary of product characteristics for Evicel® will also be updated with the new information.

Quixil® is a nationally approved drug. The marketing authorisation holder for Quixil® has chosen to withdraw Quixil® from the European market and replace it with Evicel®.

**Indication for Evicel® (human fibrinogen)**
Evicel® is used to stop bleedings and to seal tissues and blood vessels in surgery where standard surgical techniques are insufficient. It is also indicated as suture support for haemostasis in vascular surgery.

## Please report any suspected excessive use or abuse of medicinal products to the Danish Health and Medicines Authority

Suspected abuse or inappropriate excessive use of a particular medicinal product can be reported to the Authority on a special form *Problemer ved brug af medicin, medicinsk udstyr eller mistanke om misbrug* (in Danish only; English title: Problems associated with the use or suspected use of medicines or medical devices).

You can also inform the Authority using the custom form for adverse reaction reporting (in Danish only), which is available at *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*. Remember to write that the report concerns abuse.

### When is it a case of drug abuse?

Abuse of medicinal products is defined in the medicines legislation as the persistent or sporadic, intentionally excessive use of a medicinal product, accompanied by harmful physical or mental effects.

Due to new European legislation on pharmacovigilance, as of August 2012, a new and broader definition of adverse reactions has been introduced, according to which responses due to abuse of a medicinal product, which are noxious and unintended, are also considered adverse reactions.

Abuse may occur without physical and mental dependence, but most often the abuser will be mentally as well as physically dependent.

### Medicines with a known abuse potential

It is well-known that use of medicines such as strong opioid analgesics, anxiolytics and benzodiazepine-type sleeping medicines as well as stimulants of the central nervous system may lead to abuse, but this also applies to other drugs such as certain anaesthetics for human and/or veterinary use.

Apart from medicines with an already known potential for abuse, the Danish Health and Medicines Authority also wants to be advised of abuse problems involving other types of medicine – especially following marketing of new drugs.

### Focus on promethazine (e.g. Phenergan®)

The Authority thus focuses on different drugs for which abuse or excessive use may be an issue. Currently, the Authority monitors the consumption of, e.g., the substance promethazine which is sold under the name Phenergan® among others.

### Wider collaboration broadens knowledge and minimises risk

The Authority monitors doctors' prescription of the drugs that are habit-forming and have a potential for abuse, cooperating nationally and internationally to broaden our knowledge and minimise the risk of drug abuse. We can add information to the concerned summaries of product characteristics and tighten provisions for medicine dispensing. We can also include medicines in annex 1 of the Danish executive order on euphoriant substances, one of the effects being that the concerned medicines are made subject to import/export and possession controls.

## Reminder of the risk of renal impairment in association with the use of allopurinol (Allopurinol "DAK" and others)

The Danish Health and Medicines Authority has received a total of 12 reports of medicine users whose renal function was affected to different degrees in association with the administration of allopurinol. Renal impairment is a known adverse reaction from the use of products containing this active substance.

### Report of renal impairment in an elderly patient

Among other reports in October, we received an adverse reaction report concerning an elderly patient undergoing treatment with allopurinol 100 mg daily, who was hospitalised with an affected renal function with increasing blood creatinine level, dizziness, a tendency to fall, nausea and vomiting. At the time of hospitalisation, the patient was dehydrated.

Since initiation of treatment four years earlier, the patient had had a habitually elevated creatinine level of 150 µmol/l. At the time of hospitalisation, this level had increased slightly. The patient recovered after being rehydrated. However, the creatinine level did not decrease to the value it had when initiating the treatment four years earlier until after discontinuation of allopurinol.

### As a doctor you should be aware of the following:

- Among rare adverse reactions, the summary of product characteristics for allopurinol describes that patients may experience renal impairment, including interstitial nephritis, in association with the administration of this product.
- The symptoms can occur at any time during treatment. In case of symptoms of interstitial nephritis, the treatment with allopurinol should be stopped and treatment of interstitial nephritis initiated immediately.
- Caution must be exercised when dosing allopurinol in patients with pre-existing renal impairment.

**Indication for Allopurinol "DAK"**
Correction of symptomatic hyperuricaemia, including gouty arthritis (gout). It should not be initiated until at least two weeks after an attack has settled. In case of ongoing treatment, it should not be discontinued during an attack.

## Gathering knowledge of adverse reactions from the use of biological drugs in children

In recent years, there has been a substantial increase in the approval of new types of biological medicines for use in children with autoimmune diseases such as juvenile idiopathic arthritis, Crohn's disease and psoriasis.

A new report from the Danish Health and Medicines Authority shows that the Authority's adverse reaction database only comprises a few suspected adverse reactions observed in children treated with biological medicines.

Based on questionnaires filled in by parents and relatives, the report also concludes that a number of adverse reactions are not reported and that such reporting could contribute to broaden our knowledge of the treatment.

Read the entire report on the safety impact of user reports concerning biological medicines here (in Danish only): *Brugerindberetninger om biologisk medicin er vigtige for sikkerheden*

## A new report compares adverse reaction reports from medicine users and relatives with reports from healthcare professionals

The Danish Health and Medicines Authority has reviewed the adverse reaction reports received during the years 2003–2011 to clarify how reports from medicine users differ from reports from healthcare professionals and specify how such differences contribute to improving patient safety.

The comparison shows that the contribution to the total number of adverse reaction reports from reports submitted by medicine users and relatives is significant, quantitatively as well as qualitatively. In general, the reports from medicine users provide important, well-documented information.

Read the entire report here: *Adverse reaction reports from medicine users and relatives in Denmark – and comparison with reports from healthcare professionals*

## Danish Medicines Act available on our website

The Danish Medicines Act regulates the authorisation and control of medicinal products and the companies manufacturing, storing or otherwise handling medicinal products.

A new version of the Danish Medicines Act is available in English on our website: *The Danish Medicines Act*
(You can also read the Danish version here: *Lægemiddelloven*)

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