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EU's Pharmacovigilance Risk Assessment Committee (PRAC) recommends strengthening the restrictions on the use of the epileptic medicine valproate (Deprakine etc.) in women and girls

The Pharmacovigilance Risk Assessment Committee (PRAC) under the European Medicines Agency (EMA) has recommended strengthening the restrictions on the use of valproate-containing medicines for epilepsy due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

In Denmark, valproate is authorised for the treatment of epilepsy and bipolar disorder. According to the new recommendations, valproate should not be used for these indications in women and girls who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. If valproate is considered the only possible treatment option, the woman should be informed of the possible risks and the importance of using contraception. The treatment should be started and supervised by a specialist in the field.

Danish women treated with valproate

In 2013, just under 5000 women aged between 15-64 years were treated with valproate in Denmark[1].

Background leading to the new recommendations

The PRAC recommendations follow a review of available ADR data on valproate exposure during pregnancy. In its review, the PRAC also consulted patients and families who have experience with valproate treatment as well as a group of experts in the field.

Recent studies have shown that 30-40 % of pre-school children who had been exposed to valproate in the womb showed signs of developmental problems such as delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

The available data also show that children exposed to valproate in the womb are at increased risk of developing autistic spectrum disorder (around three times higher than in the general population) and childhood autism (five times higher than in the general population). There are also limited data suggesting that these children may be more likely to develop the symptoms of ADHD.

Furthermore, children of mothers who took valproate during pregnancy are at an approximately 11 % risk of malformations at birth (such as neural tube defects and cleft palate) compared to a 2-3 % risk for children in the general population.

Educational material and information

The PRAC has recommended that educational material be provided to healthcare professionals and to women prescribed valproate to inform them of these risks. The medicine's product information will also be updated.

The product information of valproate medicines available in Denmark already contains information about the risks during pregnancy, but will now be further updated to reflect the newest recommendations.

[1]The number of users in the primary sector are sourced from Medstat.

News from the EU

Monitoring of liver function during treatment with agomelatine (Valdoxan)

The European Medicines Agency (EMA) has completed a review of the benefits and risks of agomelatine (Valdoxan) for the treatment of depression, concluding that the benefits continue to outweigh the risks. However, it recommends further measures to minimise the risk of liver injury. Studies have revealed that the liver function is not monitored adequately, and consequently, the recommendations for monitoring the liver function will be tightened further.

Doctors should be aware of the following:

- Tests of the liver function should be performed in all patients before treatment, and treatment must not be initiated if transaminase levels exceed three times the upper limit of normal.
- A liver function test should be performed about 3, 6, 12 and 24 weeks after treatment has been initiated and thereafter whenever clinically indicated.
- Treatment must be discontinued immediately if transaminase levels exceed three times the upper limit of normal, or if there are symptoms or signs of potential liver injury (such as dark urine, light-coloured stools, jaundice, right upper quadrant abdominal pain, unexplained long-term fatigue).
- Patients should be informed of the symptoms suggestive of liver injury and the importance of a liver function test, and should be advised to stop treatment with agomelatine immediately and to consult a doctor if any such symptoms appear.

Valdoxan (agomelatine) was authorised in 2009 for the treatment of moderate to severe depression in adults. Agomelatine has a different mode of action and a different safety profile than the other antidepressants on the market. Agomelatine is contraindicated in patients with impaired liver function (i.e. liver cirrhosis or active liver disease) or transaminases exceeding three times the upper limit of normal. There is no documented effect of agomelatine in patients ≥75 years, and therefore agomelatine should not be used by patients in this age group.

Read the EMA's press release here:
EMA confirms positive benefit-risk for antidepressant Valdoxan/Thymanax (agomelatine)

News from the EU

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[1].

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 on the PRAC meeting in September 2014 concern the following products:

- Androgen deprivation therapy – QT interval prolongation due to long-term use.
- Chlorhexidine cutaneous solutions – chemical injury including burns when used in skin disinfection in premature infants.
- Imatinib – decreased estimated glomerular filtration rate.
- Leuprorelin – medication error due to wrong technique in drug usage process.

See EU's list of recommendations on safety signals:

PRAC recommendations on signals.

[1]The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Ethambutol and effects on vision

In August, the Danish Health and Medicines Authority (DHMA) received an ADR report about an elderly patient who had been treated with ethambutol (Myambutol) for an atypical mycobacterial pulmonary infection. After ten months' treatment, the patient was diagnosed with optic neuritis after the patient's eyesight had been declining gradually. Treatment was discontinued, and the patient is now recovering.

Number of suspected adverse reactions to ethambutol

Year	2008	2009	2010	2011	2012	2013	2014
Total number of reports. (Number of reports of optic neuritis)	1 (0)	3 (1)	3 (1)	0	1 (0)	3 (0)	3 (3) *

Table 1: The number of ADR reports in the period 2008-2014 (*ADR reports are included up until 31 August 2014).

All eye-related ADR reports (five in total) in the period 2008-2014 concerned optic neuritis. In the summary of product characteristics for ethambutol-containing medicines, decreased visual acuity and optic neuritis are described as common adverse reactions (> 1/100 and <1/10).

Doctors should be aware of the following:

- Ethambutol can cause decreased visual acuity and impair colour vision, occurring as a result of optic neuritis and/or retrobulbar neuritis.
- This adverse reaction is dose-related, but it may occur at doses as low as 15 mg/kg body weight and depends on the duration of treatment. Usually, the reaction is reversible if ethambutol treatment is discontinued at onset of symptoms.
- Visual acuity will usually return to normal in a matter or weeks or months after discontinuation of ethambutol treatment. In rare cases, it will take 12 months or longer to recover. There have been reports of irreversible blindness.
- Some patients have resumed ethambutol treatment after a recovery without experiencing a relapse with loss of visual acuity.
- Visual acuity should be evaluated before treatment is initiated and regularly during treatment at least once every month. An ophthalmic examination should include ophthalmoscopy, perimetry and a test of the ability to distinguish colours.

Indications for ethambutol:
Tuberculosis. Myambutol should always be given in conjunction with another anti-tuberculosis drug.

Safety of products containing botulinum toxin (Botox® etc.) and fillers for cosmetic treatment

Lately, cosmetic treatment and the safety of the products used in this particular type of treatment have been debated in the media. We have therefore taken a look at how many and what kind of adverse reactions have been reported to us related to products used in cosmetic treatment.

Products for cosmetic treatment

- **Botulinum toxin** is a medicine which has the effect of a neurotoxin. It is produced by the anaerobe bacteria clostridium botulinum. The toxin acts by blocking the release of acetylcholine and hence inhibits the neuromuscular transmission, which leads to muscle paralysis. The effect is not lasting, but reverses over a couple of months.

- **Fillers** are classified as medical devices. Fillers refer to a variety of different substances that are injected in or under the skin to make up for lack of fatty tissue, to even out wrinkles or other lack of tissue and to add fullness. Traditionally, fillers are grouped in non-permanent fillers that are absorbed by the body, and permanent fillers (including semi-permanent fillers) that are slowly absorbed by or remain in the body.

ADR reports related to treatment with botulinum toxin

The DHMA has received a total of 54 reports of suspected adverse reactions to botulinum toxin-containing products. The vast majority of them (43 reports) concern use in medical indications. In nine of the reports, botulinum toxin is indicated as having been used for cosmetic treatment. In two of the reports, there is no mention of indication.

Four of the nine reports on botulinum toxin used in cosmetic treatment describe serious adverse reactions[1], including allergic reactions, vitreous body prolapse and an increased tendency for infections.

The risk of allergic reactions is known, and the treatment is contraindicated in patient with known hypersensitivity to botulinum toxin type A or to any other of the excipients.

Vitreous body prolapse is not described in the medicine's product information.

Whereas the risk of local infections and influenza-like symptoms are well-known for botulinum toxin, no increased tendency for subsequent systemic infections are described in the summary of product characteristics.

In other non-serious ADR reports where botulinum toxin has been used cosmetically, symptoms have been described such as local reactions, rash and oedema, all of which are expected from injections. Influenza-like symptoms with headache and fever have also been reported and are described in the summary of product characteristics.

It is emphasised in the product information that botulinum toxin must only be given by doctors with appropriate qualifications and knowledge about the treatment[2] and ability to use the available equipment.

[1] A serious adverse reaction is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Reports related to incidents with fillers

The DHMA has received a total of 48 reports describing incidents with fillers since 1998 when the directive on medical devices and system for incident reporting was implemented.

Most of the reports describe serious incidents such as infections as well as swelling and/or formation of nodules at the treatment area. Less serious incidents have also been reported, e.g. fever, local redness or tenderness.

Mostly known incidents with fillers are reported

Most of the incidents reported to the DHMA are described in the summary of product characteristics of several of the fillers that are on the market.

It appears from these fillers' product information that their immediate adverse reactions are redness, local swelling, itching and tenderness, which usually abate in the course of two days. Infections at the injection site and allergic reactions to the filler material may occur. Late-onset adverse reactions after treatment with non-permanent fillers are rare. Only in a few cases have infections and development of disfiguring scars been seen.

Serious adverse reactions are especially seen after treatment with permanent fillers, including the development of connective tissue formation as well as disfiguring and debilitating scars. Such reactions may develop years after treatment and occur because the body reacts to the injected foreign material. The problems of scar tissue development are not only cosmetic, but can be painful and could restrict the natural movement of for example the lips, in which case surgical removal is often necessary.

Infection could occur in or around the injected filler. This could also occur many years after treatment. It is possible that the filler may move away from the original injection site due to a combination of factors: the filler's plasticity and outside pressure or muscle pressure.

[2]According to section 4(xviii) of the Danish executive order on cosmetic treatment, doctors in Denmark can become registered to perform botox treatment if they have qualified as a specialist in dermatovenereology, neurology (disorders of the nervous system), ophthalmology or plastic surgery.
At the beginning of 2013, the Danish Health and Medicines Authority amended section 4 of the Danish executive order on cosmetic treatment so that doctors in addition to the relevant specialist training must document relevant qualifications to be registered to perform cosmetic treatment. With this amendment, the Danish Health and Medicines Authority has made no attempt to change the registration requirements significantly. If a medical specialist as part of his or her education is trained to perform one of the 25 treatments (listed in section 4), this will generally be enough for the doctor to become registered to perform the treatment in question without having to provide further documentation.

According to section 5, doctors with permission to independently practice medicine and with documented, relevant qualifications can, after a specific assessment of their qualifications, receive permission from the the Danish Health and Medicines Authority to perform the cosmetic treatments named in section 4.
The Danish Health and Medicines Authority wants to point out that the exemption defined in section 5 is either reserved for doctors who at the time when the rules entered into force possessed the qualifications to perform the treatment listed in section 4 or for doctors who over a long period of time, e.g. abroad, have acquired adequate experience and routine to perform the treatment they apply for. It is primarily considered a transitional provision for doctors who were already performing cosmetic treatments when the rules entered into force and doctors (Danish as well as foreign) with adequate experience and routine to perform the treatment applied for.

Marketing of botulinum toxin for cosmetic treatment

There are several botulinum toxin-containing medicines in Denmark. The first medicines with botulinum toxin were authorised for medical indications in the middle of the 1990s, but treatment of cosmetic indications were not authorised until about 10 years ago. The medical indications for botulinum toxin are neurological diseases such as spasticity, bladder disease and hyperhidrosis.

Marketing of fillers

Fillers are marketed as medical devices. Unlike medicines, medical devices need not be authorised by way of a marketing authorisation granted by either the DHMA or the European Commission. Instead they are certified by a notified body in compliance with the rules on medical devices.

Indications for medicines used in cosmetic treatment that contain botulinum toxin:

Vistabel®
When the severity of the following facial lines has an important psychological impact in adult patients, Vistabel is indicated for the temporary improvement in the appearance of:

- moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines),
- moderate to severe lateral canthal lines (crow's feet lines) seen at maximum smile,
- moderate to severe crow's feet lines seen at maximum smile and glabellar lines seen at maximum frown when treated simultaneously.

Azzalure®
Temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adults under 65 years, when the severity of these lines has an important psychological impact on the patient.

Indication for fillers:

It is not possible to list the product names of the fillers used, as the market is changing constantly. However, hyaluronic acid is the most common substance in non-permanent fillers. It applies to all fillers that their effect is comparable to the insertion of implants.

- Non-permanent fillers are primarily used for the treatment of minor wrinkles and scars as well as for lip augmentation. The effect usually lasts for three to six months.
- Permanent/semi-permanent fillers are primarily used for the treatment of severe wrinkles or deep scars and significant defects of the skin.

Short news

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:

- **Parenteral nutrition with amino acids, carbohydrates and fat (Olimel/Olimel Perifer):**
  – Reduction of maximum infusion rate per hour for children aged 2 to 11 years
  – Medication error: Reminder of the importance of correct preparation and administration.

- **Anti-HIV medicine emtricitabine (Emtriva):**
  Risk of leaking: Recommendation to check the bottles before use.

- **Contrast agent sulphur hexafluoride (SonoVue):**
  Revised contraindications, warnings and precautions for use

The DHPCs are available in Danish at the DHMA website: *List of circulated DHPCs.*

Domperidone and new dosage recommendations – clarification of DHPC

In August 2014, a DHPC was sent out to doctors with new recommendations to restrict the use of domperidone in response to a new benefit-risk profile. Unfortunately, the DHPC mentioned no dosage recommendation for suppositories, even though it appeared from the DHPC heading.

The dosage recommendations for suppositories are described in our article in *Danish Pharmacovigilance Update, April 2014.*

The dosage recommendations are as follows:

- In adults, children and adolescents weighing 35 kg or more, the recommended maximum dose of domperidone is 10 mg tablets three times daily or 30 mg as a suppository twice a day.

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