Danish Pharmacovigilance Update

Year 2 #10
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Use of medicines involving a risk of serious and life-threatening skin reactions

Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are serious and, in some cases, life-threatening skin reactions. It is well-known that in rare cases, specific types of medicine can cause SJS and TEN, and the prognosis for patients inflicted with these serious adverse reactions depends on an early detection followed by an immediate discontinuation of treatment.

The European Pharmacovigilance Working Party has reviewed the product information for a number of medicinal product groups – including specific active substances with a known risk of SJS/TEN – and has prepared joint recommendations for these:

- Doctors should inform their patients to pay attention to skin reactions, especially within the first weeks of treatment.
- In the event of symptoms of SJS/TEN (progressive rash, often with blisters or mucosal lesions), treatment with the medicine must be discontinued immediately.
- Patients with a history of SJS/TEN during treatment with a specific medicine should not be prescribed this medicine again.

For further information, please read the PhVWP monthly report *here*.

Medicines with known risks of SJS and TEN, which were included in the review, are:

- Allopurinol
- Antiepileptics: carbamazepine, lamotrigine, phenobarbital and phenytoin
- Analgesics: meloxicam, piroxicam and tenoxicam
- Antiviral agents: nevirapine
- Sulfonamides: sulfadiazine, sulfadoxine, sulfafurazole, sulfamethoxazole and sulfasalazine.

European Medicines Agency to investigate the possible connection between orlistat and rare cases of severe liver toxicity

The European Medicines Agency (EMA) has started reviewing the possible connection between orlistat, used for the treatment of overweight, and the occurrence of severe liver damage.

The risk of liver reactions involved in the use of medicines containing orlistat has been continuously monitored by the Committee for Medicinal Products for Human Use (CHMP), and the summaries of product characteristics already contain information about certain liver reactions.

The latest analysis of the issue showed that during the period 1997 to 2011, 21 cases of severe liver toxicity following the use of orlistat were reported worldwide. The number of reports should be seen in the light of a total of 38 million patients. This is thus not a strong signal, but a causal relationship cannot be ruled out.

The EMA's investigation will include Xenical® (orlistat 120 mg) and Alli® (orlistat 60 mg) as well as a number of other products either already approved or in the process of becoming so.

In Denmark, there have been no reports of serious incidents concerning liver toxicity in connection with the use of orlistat.

For further information, please visit the EMA website *here*.

EMA completes review of peritoneal dialysis solutions from Baxter A/S

The European Medicines Agency (EMA) has now completed its investigation of the production processes at Baxter's Castlebar plant in Ireland, following the discovery in December 2010 of endotoxins in batches of the dialysis solutions Extraneal Viaflex®, Nutrineal Viaflex® and Dianeal®.

In order to minimise the future risk of endotoxins in the production of peritoneal dialysis solutions, a number of measures have been taken at the Castlebar plant, which have improved production and the quality of the dialysis solutions. Furthermore, the EMA has prepared some recommendations to ensure the EU supply of dialysis solutions if similar problems should occur in the future.

The Irish Medicines Board will inspect the Castlebar plant during October, and the plant will then resume dialysis solution production. The products will be continuously tested, and the plant will be closely monitored.

For further information, please visit the EMA website *here*.

Product information for Revlimid® to be updated

The European Medicines Agency (EMA) has completed an investigation of Revlimid®, which was launched on the basis of data showing a higher incidence of new cancer cases in patients treated with Revlimid® compared to patients not having undergone treatment with this medicine.

The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Revlimid® for the approved indication continue to outweigh its potential risks – including the risk of new cancer cases. However, the Committee recommended updating the product information.

For further information, please visit the EMA website *here*.

Revlimid® is used for the treatment of multiple myeloma

The Danish Medicines Agency has received a report of a death in connection with use of the smoking cessation product Champix®

In September 2011, the Danish Medicines Agency received an adverse reaction report concerning a woman in her thirties who had been taking the smoking cessation product Champix® for seven weeks.

The woman was hospitalised with acute chest pains. An ECG showed that the woman had an acute myocardial infarction which caused her death.

The Agency has followed up on the report which indicates that, beyond smoking and using contraceptive pills, the woman was not further susceptible to cardiovascular disease.

It cannot be ruled out nor confirmed that Champix® caused the woman's death.

The summary of product characteristics for Champix® describes that myocardial infarction has been observed in a small number of persons, but the frequency is unknown.

As described in the Danish Pharmacovigilance Update from August 2011, the European Medicines Agency (EMA) recently assessed a new study which indicates that Champix® may be linked to a risk of cardiovascular problems. The conclusion was that the benefits of Champix® still outweigh the potential risks, but the EMA has asked the marketing authorisation holder to add more information about cardiovascular adverse reactions to the product information.

Updating of the summary of product characteristics with further information about potential cardiovascular adverse reactions was commenced before the case in question.

See the Danish Pharmacovigilance Update from August *here*.

List of medicines most frequently involved in serious adverse drug events to help minimise risks in the medication process

A new survey made by a working group associated with the Danish Medicines Agency's Network for the Prevention of Medication Errors has demonstrated that more or less the same medicine groups have been involved in situations which have led to adverse events from the 1970s until today.

The survey shows that the use of the medicines during certain steps of the medication process may pose a risk of an adverse event. For instance, units such as mg and ml may be confused in connection with dosing of medicines.

A tool in the day-to-day work with medication of patients

On the basis of the survey, two lists have been prepared of medicines involved in risk situations – sorted by active substance and medicine group, respectively.

The Danish Medicines Agency and the working group behind the survey hope that the lists may now become a useful tool in the day-to-day work on reducing risks in connection with medication in the health sector – hopefully a tool which can help healthcare professionals pay attention to the medicines which require extra safety measures and thus contribute to improving patient safety.

Read more in the report on medicines most frequently involved in serious adverse drug events *here*.

See the list of medicines most frequently involved in serious adverse drug events *here*.

New restrictions in use, further contraindications and warnings for Multaq® (dronedarone)

Following several instances of liver damage in patients undergoing treatment with dronedarone – including two cases of liver failure which required a transplant, the Committee for Medicinal Products for Human Use (CHMP) launched an investigation at the end of January 2011 of the benefits and risks afforded in the treatment with Multaq® – see *Pharmacovigilance Update, February 2011*.

On the basis of several pulmonary and cardiovascular adverse reaction reports, the investigation was expanded to also include pulmonary and cardiovascular safety. The reports concerning cardiovascular adverse reactions were submitted in connection with the PALLAS study, which investigated high-risk patients with chronic atrial fibrillation (AF). The study was prematurely terminated due to a significant predominance of cardiovascular related deaths and cardiovascular hospitalisations and cases of apoplexy in the dronedarone group. See *Danish Pharmacovigilance Update, August 2011*.

The conclusion of the CHMP investigation was that the benefits still outweigh the potential risks of Multaq® for a limited patient group under close monitoring. Overall, new restrictions in the indication area are recommended as well as further contraindications and warnings for patients prescribed this medicine.

New restrictions for the use of Multaq®:

New restrictions in the indication area

- Multaq® is now only indicated for clinically stable adult patients with paroxysmal or permanent atrial fibrillation (AF) for the maintainance of sinus rhythm after successful cardioversion.
- Because of the adverse reaction profile, Multaq® should only be prescribed when other treatment options have been considered.
- Treatment with Multaq® should only be initiated and monitored by a specialist.

New contraindications – Multaq® is now contraindicated for patients with:

- Unstable haemodynamic conditions.
- History of, or current, heart failure or left ventricular systolic dysfunction.
- Permanent AF (i.e. duration ≥6 months or unknown, and attempts to restore sinus rhythm no longer considered by physician).
- Liver and lung toxicity related to previous use of amiodarone.

New warnings

- If the patient develops one of the conditions for which Multaq® is contraindicated, treatment with Multaq® should be discontinued.
- Patients currently undergoing treatment with Multaq® should have their treatment assessed at their next control to ensure that they are still suitable for treatment with Multaq® in accordance with the revised summary of product characteristics.
- Patients receiving Multaq® should be monitored closely during treatment with regular assessment of their heart, liver and lung function.
- To increase the safety related to the use of Multaq®, prescribing doctors should also note the following new monitoring requirements:

Cardiovascular monitoring:

- Patients should receive regular cardiac examinations, including an ECG at least every six months, in patients undergoing treatment with Multaq®. If AF reoccurs discontinuation of dronedarone should be considered for these patients.
- Discontinue treatment if the patient develops permanent AF.
- Patients should be carefully evaluated for symptoms of heart failure during treatment.
- Patients should be appropriately anticoagulated as per clinical AF/anticoagulant guidelines. International Normalised Ratio (INR) should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per the prescribing information for these products.

Hepatic monitoring:

- Liver-function tests should be done: before starting treatment with dronedarone; after one week of treatment; after one month of treatment; then every month for six months; at month 9; at month 12; and periodically thereafter.

Renal monitoring:

- As a minimum, plasma creatinine values should be measured before and seven days after initiation of dronedarone.

Pulmonary monitoring:

- Cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported in association with Multaq®. Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity. If pulmonary toxicity is suspected during treatment, relevant lung examinations should be considered and treatment discontinued if confirmed.

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> Patients should be instructed to contact their doctor in the event of newly occurring cardiovascular or pulmonary symptoms or in case of signs of hepatic effects.

In addition to the above, doctors should pay particular attention to the possibility of drug interactions and the potential need for dosage adjustment when Multaq® is used concurrently with other medicines, including anticoagulants and digoxin.

A DHPC (Direct Healthcare Professional Communication) letter informing about the new restrictions in the indication area, further contraindications and warnings was issued to relevant doctors in October.

At the earliest possible opportunity, the summary of product characteristics for Multaq® will be updated with the changes above.

For further information, please visit the EMA website *here*.

Since January 2010 when Multaq® was marketed in Denmark, and up to and including August 2011, 1171 people have undergone treatment with this medicine.

The Danish Medicines Agency has received 21 adverse reaction reports related to the use of Multaq®. No instances of liver damage and lung toxicity have been reported in Denmark.

Adverse reactions in connection with the childhood immunisation programme in the first half of 2011

The Vaccinationspanelet (Danish medical scientific vaccination panel), represented by the Danish Medicines Agency, the Danish National Board of Health and the Danish State Serum Institute, convenes once a quarter to assess the suspected adverse reactions reported from vaccines – primarily from vaccines involved in the childhood immunisation programme.

The adverse reaction data from the first half of 2011 are shown below.

The first half of 2011 saw no changes in the Danish routine childhood immunisation programme. It is estimated that the figure of 80-90 per cent of children being vaccinated, depending on the vaccine, is unchanged.

Between 1 January and 30 June 2011, the Danish Medicines Agency received a total of 58 reports containing a total of 212 potential adverse reactions related to a total of 73 vaccinations (some children received more than one vaccine at the same time). Of these, 33 adverse reactions in 11 patients were classified as serious*.

The majority of the suspected adverse reactions reported were well-known, such as local reactions at the injection site, fever and general malaise – including nausea and fatigue.

The distribution of the number of non-serious and serious adverse reactions for the different vaccines involved in the childhood immunisation programme in the first half of 2011 can be seen from the table.

Only two reports concerned eczema following vaccination with Gardasil® – this should be compared to 2009 when there was a focus on eczema as a suspected adverse reaction from Gardasil® and therefore many reports. Unexpected adverse reactions classified as non-serious were abnormal hair growth, urination difficulties in three children, impetigo in two children and chest pains in one patient.

The serious adverse reactions were:

1. One case of acute disseminated encephalomyelitis (ADEM) one month after measles, mumps and rubella (MMR) vaccination in a 13-year-old boy. The boy is recovering, but at the time of follow-up, he was not yet in his habitual state. A connection to the vaccine cannot be ruled out.

2. One case of herpes zoster following vaccination with MMR and Gardasil® 28 days after vaccination. A correlation is deemed to be less likely.

3. One case of suspected erysipelas in which a child, following diphtheria-tetanus-pertussis-polio booster developed severe redness and swelling of the upper arm. The child was hospitalised for observation. However, blood tests did not reveal an infection, and redness/swelling disappeared.

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Vaccine	Total no. of non-serious adverse reactions per vaccine	No. of serious adverse reactions categorised as serious*
Diphtheria vaccine "SSI"	19	0
Pneumovax	1	0
Diphtheria-tetanus (DTa) booster	10	0
DTa-pertussis-polio (DTaP-IPV) booster	9	4
DTaP-IPV	1	0
DTaP-IPV/Act-Hib	29	6
Act-Hib	1	0
Gardasil®	45	4
Prevenar	8	3
Prevenar 13	8	3
Priorix®	16	13
Tetanus®	32	0
Total	**179**	**33**

* **Definition of a serious adverse reaction:**
- *The patient was hospitalised or had the hospital stay extended – i.e. any person who has been briefly hospitalised with an adverse reaction will have been classified as having a serious adverse reaction.*
- *The patient was in a life-threatening condition.*
- *The patient became disabled or suffered a considerable functional impairment*
- *The patient died.*
- *Malformations or congenital malformations because either mother or child was vaccinated.*

> 4. Monoarthritis (swollen joint) after Priorix® vaccination; no other etiology was found. The symptoms disappeared spontaneously.

5. Suspicion of infantile spasms in a child of three months which, following vaccination with Prevenar and diphtheria-tetanus-pertussis-polio-hib(meningitis) (DTaP-IPV/Act-Hib), developed a fever and twitches resembling infantile spasms after seven hours. The follow-up showed that the child was well at the time of discharge and that the episode was considered to be a case of fever caused by the vaccine and accompanied by quivering.

6. One case of fever cramps following vaccination with Prevenar and DTaP-IPV/Act-Hib. Little information concerning temporal relation.

7. One case in a 2-year-old boy of fever and rash ten days after vaccination with Priorix® and Twinrix®. The coagulation parameters were found to be elevated. Rash and fever may present after Priorix® vaccination, but there are no previous reports of effect on coagulation parameters, and therefore a correlation is deemed to be less likely.

8. One case of rubella-like rash and parotitis of the right side two days after vaccination with Priorix® in a 2-year-old boy. Enlargement of the salivary gland (parotid gland) is a known adverse reaction from the Priorix® vaccine, but two days after vaccination seems to be early, and rubella-like rash is more often seen after approx. ten days. Swelling of salivary glands and rash may also present in viral infections, e.g. coxsachie virus.

9. One case of facial paresis in a 12-year-old girl, occurring on the same night that the first Gardasil® and Priorix® vaccine were administered. No microbiological etiology found for the paresis. Patient recovered fully.

10. One case of uncomplicated fever cramps ten days after DTaP-IPV/Act-Hib + Prevenar 13 in a 5-month-old boy. Normally, fever and thus fever cramps will present within the first days after vaccination with DTaP-IPV/Act-Hib + Prevenar 13, and it is therefore in this case deemed less likely that there is a connection between the fever cramps and the vaccinations.

11. 5½ -month-old boy born prematurely with GA 26 weeks receives a vaccination with DTaP-IPV/Act-Hib and Prevenar13 and four days later develops symptoms of a cold (nasopharyngitis with mucus production) necessitating hospitalisation. Patient recovered. Virus examinations for the most common viruses were negative. Mucus secretion is not a known adverse reaction from the vaccines.

Conclusion

In comparison, the Danish Medicines Agency received 168 reports involving a total of 468 suspected adverse reactions in 2010 in connection with the childhood immunisation programme. The number of reports thus appears to be stable for the first half of 2011. Among the suspected adverse reactions categorised as serious, particularly one case of acute disseminated encephalomyelitis (ADEM) after Priorix® vaccination should be noted, in which symptoms are still present. This was an isolated case. For the remaining reports categorised as serious, all patients have recovered.

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