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Drug Analysis Prints involving data from more than 14,000 Danish adverse reaction reports available at the Danish Health and Medicines Authority's website

In February, the Danish Health and Medicines Authority published the first 14 of approx. 1,000 adverse drug reaction listings, called Drug Analysis Prints (DAP), containing information on adverse reaction reports from doctors, patients and relatives.

On 9 May, the remaining DAPs were published on the website: *Drug Analysis Prints: Adverse reactions reported*.

Each DAP contains a list of the adverse reactions reported for a specific active substance.

The almost 1,000 DAPs include data from more than 14,000 adverse reaction reports, containing a total of more than 39,000 specific reactions.

Helps direct focus towards safety issues

The DAPs primarily provide an overview of the suspected adverse reactions reported to the Danish Health and Medicines Authority, but also of the development in the scope of reports submitted. They only contain information about suspected adverse reactions, and it has therefore not been documented that the adverse reactions are caused by the drug in question. However, the Danish Health and Medicines Authority believes that these documents may help, e.g., scientists focus on safety issues which require further investigation.

A doctor would also be able to use the DAPs to check for previous adverse reactions reported for an active substance which the doctor suspects of causing adverse reactions.

Drug Analysis Prints (DAP) are anonymised extracts from the Danish Health and Medicines Authority's adverse reaction database. In the DAPs, the adverse reaction reports are distributed by system and organ class, meaning that suspected adverse reactions related to, e.g., mental disorders are grouped together.

The DAPs are in English and contain Danish reports submitted from 2007 and later.

The documents are updated monthly.

Isotretinoin (Roaccutan® etc.) for the treatment of severe acne, and adverse reaction reports related to psychiatric symptoms

A search in the Danish Health and Medicines Authority's adverse reaction database for the period between September 1985 and April 2012 shows that we received 276 adverse reaction reports related to isotretinoin (Roaccutan®*) for external and systemic use. The Danish Health and Medicines Authority has analysed the reports submitted for isotretinoin related to psychiatric adverse reactions.

Majority of reports related to psychiatric adverse reactions

Reports on psychiatric adverse reactions make up 120 out of the 276 reports submitted. All reports on psychiatric adverse reactions – with the exception of eight for which the drug formulation has not been stated – are related to isotretinoin capsules for oral use. Of the 120 psychiatric adverse reaction reports, 94 were reported by doctors, the rest by non-healthcare professional consumers.

The most frequently reported adverse reaction is depression, accounting for 80 of the 174 psychiatric adverse reactions comprised by the 120 reports. The ten most frequently reported adverse reactions are shown in Table 1.

Table 1: Psychiatric adverse reactions reported

	Volume
Depression	80
Anxiety	10
Aggression	8
Depressive symptoms	6
Suicide attempts	6
Depressed mood	5
Suicidal thoughts	5
Affect lability	4
Confusion	3
Mood swings	3
Psychotic symptoms	3

Psychiatric adverse reactions described in the summary of product characteristics for isotretinoin

The types of psychiatric adverse reactions reported, see Table 1, are consistent with the adverse reactions described in the summary of product characteristics for isotretinoin.

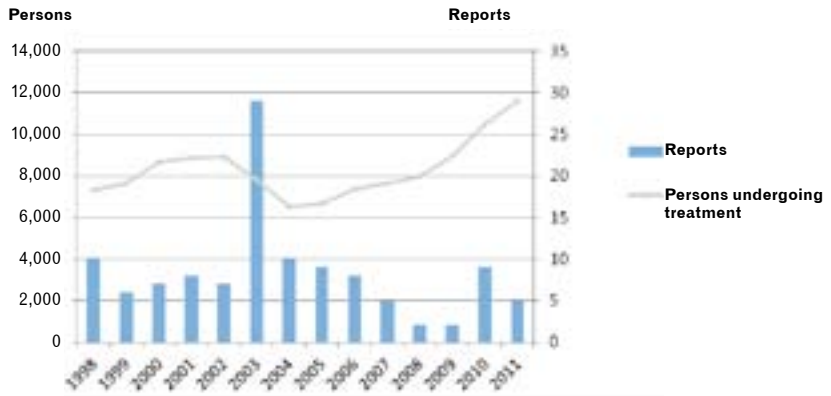
- The product information lists reports on depression, major depression, anxiety, aggressive tendencies, mood swings, psychotic symptoms and, in very rare cases, suicidal thoughts, suicide attempts and completed suicides in patients treated with isotretinoin.

- Particular care should be taken in relation to patients with a history of depression. All patients should be checked for symptoms of depression and, if necessary, be referred to appropriate treatment. However, it is not certain that discontinuation of treatment with isotretinoin will improve the symptoms, and further psychiatric or psychological assessment may therefore be required.

Reports on psychiatric adverse reactions and no. of isotretinoin users

From 1998 to 2011, the reporting frequency was stable at no more than >

Figure 1. Reports on psychiatric adverse reactions and no. of isotretinoin users



> ten annual reports, with the exception of 2003. In 2003, we received 29 reports related to psychiatric adverse reactions, and the number of users of isotretinoin dropped, see Figure 1.

The large number of reported psychiatric adverse reactions reported in 2003 may be due to the product information for isotretinoin being updated with information on psychiatric adverse reactions. This may have stimulated increased reporting on this specific type of adverse reactions.

The number of users of isotretinoin has been increasing since 2004. Since 2008, the number of users has increased by 46% from 7,956 users in 2008 to 11,580 users in 2011.

More than half of reports on psychiatric adverse reactions received relating to adolescents between 15-25 years

More than half of the reports on psychiatric adverse reactions received, 74 of the 120 (62%), are from users in the age group 15-25 years, see Figure 2, reflecting that this age group contains the primary users of the drug. In 2011, 64% of all users were found in this age group, and the age distribution for psychiatric symptoms reported therefore gives no cause for concern.

Product information still adequate

Detailed analysis of the relatively large number of psychiatric adverse reactions for isotretinoin shows nothing alarming in the number or types of adverse reactions reported. The information on psychiatric adverse reactions in the summary of product characteristics is still deemed to be adequate.

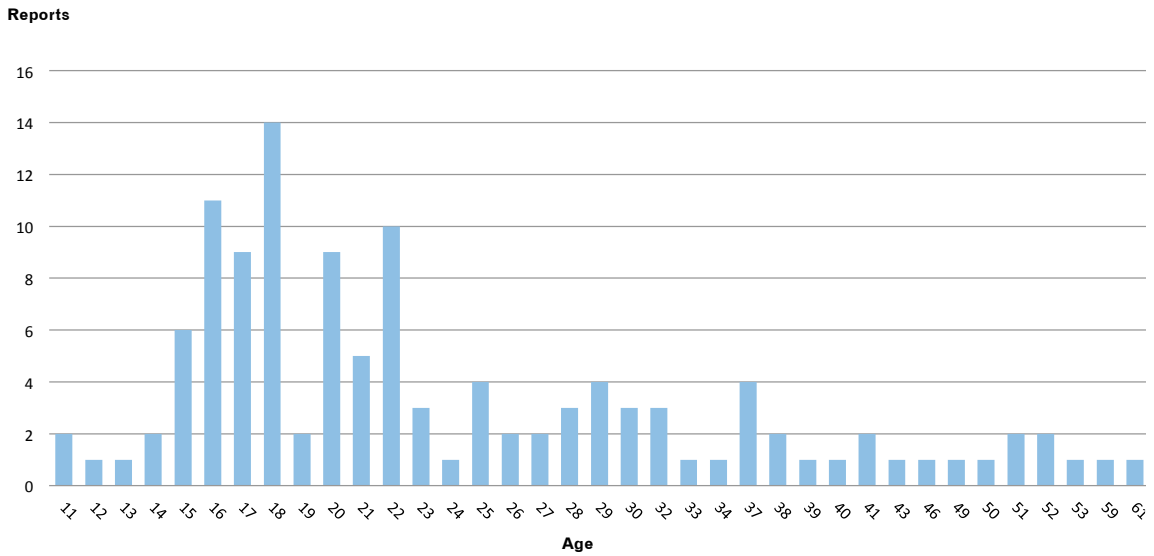
In themselves, psychiatric issues and acne pose complex problems. Psychiatric factors such as poor well-being may worsen acne due to emotional stress, and in return, untreated acne and the potential social consequences thereof may lead to various psychiatric symptoms.

Even though several scientific studies have been unable to confirm a correlation between treatment with isotretinoin and psychiatric adverse reactions, these studies have, on the other hand, not formed a basis for completely dismissing such correlation. The information in the summary of product characteristics is therefore maintained in its current form.

Advice for doctors

The Danish Health and Medicines Authority wants to call attention to the increasing consumption of oral isotretinoin and will continue to closely monitor the development within adverse reactions and consumption. It is therefore important for doctors and patients to continue reporting on adverse reactions. >

Figure 2. Age distribution for reports related to psychiatric adverse reactions



> Doctors must carefully assess advantages and disadvantages of starting up isotretinoin treatment for patients with a history of depression.

You can report adverse reactions at *report a side effect or incident*

You can find a summary of product characteristics for isotretinoin capsules at *www.produktresume.dk*.

* The medicinal product Roaccutan® has been deregistered in Denmark, but generic isotretinoin products are available on the market.

Isotretinoin has been licensed since September 1985 in Denmark. The drug is available as oral capsules for systemic use and as a gel for external use.

Indication for isotretinoin
Isotretinoin gel is indicated for the treatment of acne vulgaris, whereas isotretinoin capsules are indicated for the treatment of severe acne (such as nodular acne, acne conglobata or acne with a risk of permanent scarring) with resistance to adequate standard treatment with systemic antibacterials and local treatment.

Risk of developing acute and chronic pulmonary changes in treatment with Nitrofurantoin®

In March 2012, the Danish Health and Medicines Authority received a report on an elderly patient developing pulmonary fibrosis following treatment with Nitrofurantoin®.

The patient had suffered repeated urinary tract infections and was undergoing long-term treatment (18 months) with Nitrofurantoin®. The patient developed pulmonary fibrosis which was verified by a CT scan of the patient's lungs.

The Danish Health and Medicines Authority has received a total of 73 reports of patients developing fibrosis in connection with Nitrofurantoin® treatment.

It is important to monitor all patients undergoing long-term treatment with Nitrofurantoin® for changes in their pulmonary function, and Nitrofurantoin® should be discontinued at the first signs of change.

The summary of product characteristics for the product states that it may cause acute and chronic pulmonary changes:

- Acute pulmonary changes are dosage-independent. Sensitisation does not occur until 1-2 weeks after commencing treatment. The clinical symptoms normally disappear quickly after discontinuation.
- Chronic pulmonary changes are far more rare than acute changes and are most often observed in elderly patients. Chronic pulmonary changes are not always reversible.

Indication for Nitrofurantoin®
The indication for Nitrofurantoin® is urinary tract infections caused by bacteria sensitive to Nitrofurantoin®.

Risk of developing atrioventricular block under treatment with Gilenya®

In April 2012, the Danish Health and Medicines Authority received two reports related to the product Gilenya®, according to which patients, in the very day they were given the first product dose, developed an atrioventricular block (AV block).

One patient developed a first-degree AV block, the other a second-degree AV block. According to the reports, both patients have recovered fully.

The Danish Health and Medicines Authority has not received any other reports on patients developing AV block in connection with administration of Gilenya®. However, we have received two reports according to which patients developed a reduced heart rate immediately after administration of the product.

As it is a known fact described in the product information that Gilenya® may be associated with a risk of AV block, the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency, EMA, updated the recommendations for the use of Gilenya® (fingolimod) at its meeting 16-19 April 2012.
You can read more about this at our website: *Gilenya (fingolimod) – new recommendations aimed at reducing the risk of heart-related adverse reactions*.

Indication for Gilenya®
Since March 2011, Gilenya® has been licensed for the treatment of patients with multiple sclerosis and high disease activity in spite of treatment with beta-interferon, or for patients with severe progressive relapsing/remitting multiple sclerosis.

Tacrolimus (Protopic®) and the risk of malign conditions

Recently published epidemiological studies (see references 1,2,3) have indicated a potential risk of cutane T-cell lymphoma in patients undergoing treatment with topical calcineurin inhibitors, including tacrolimus ointment (Protopic®).

Long-term systemic exposure to intensive immunosuppression followed by systemic administration of calcineurin inhibitors – combined with other systemic immunosuppressants – is associated with an increased risk of developing lymphoma and skin malignancies. Furthermore, cases have been reported of malignant conditions, including other types of lymphoma and skin cancer in patients undergoing treatment with Protopic®.

In agreement with the European Medicines Agency, EMA, and the company, a study has been planned with a view to further investigating these risks.

The Danish Health and Medicines Authority has received a total of 16 reports of suspected adverse reactions from the use of Protopic®, but none of the reports involve malignant conditions.

The number of patients undergoing treatment with Protopic® 0.03% and 0.1%, respectively, in various age groups is shown in the table below. The table reveals that the treatment is also used for children under the age of 2, and that the maximum Protopic® dose (0.1%) is likewise used for the treatment of children.

No. of patients undergoing treatment with Protopic® 0.03% and 0.1%

Name of drug	Age group	No. of users
Protopic® (0.03%)	0-1 years	272
Protopic® (0.03%)	2 years	230
Protopic® (0.03%)	3-16 years	1.113
Protopic® (0.03%)	17+	1.652
Protopic® (0.1%)	0-1 years	85
Protopic® (0.1%)	2 years	98
Protopic® (0.1%)	3-16 years	1.524
Protopic® (0.1%)	17+	9.414

On the basis of current knowledge, the Authority wants to draw attention to the following risk-reducing measures for treatment with Protopic®:

- Protopic® should only be used in patients with moderate to severe atopic dermatitis who do not respond satisfactorily or are intolerant to conventional treatments such as topical corticosteroids.
- Protopic® should not be prescribed to patients under the age of 2. The effect of treatment with Protopic® on the development of the immune system in children under the age of 2 has not been established.
- Only the low-strength Protopic® ointment, i.e. 0.03%, should be used for children aged 2-16.
- Protopic® ointment should not be applied to lesions considered to be potentially malignant or premalignant.

Doctors should also note the following recommendations:

- If Protopic® is used for the treatment of active outbreaks (twice daily), the treatment should continue for an extended period of time. If there are no signs of improvement after 2 weeks of treatment, alternative treatment options should be considered.
- In the case of maintenance treatment (twice weekly), treatment response and the need for continued treatment should be assessed. After 12 months of treatment, the patient's clinical condition should be evaluated with a view to assessing whether the maintenance treatment should be continued. In children aged 2-16, treatment with Protopic® should be discontinued after 12 months to assess the child's need for continued treatment.
- Occurrence of lymphadenopathy when initiating treatment should be investigated and monitored. Patients undergoing treatment with Protopic® who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy disappears. In the event of permanent lymphadenopathy, the etiology of the lymphadenopathy should be assessed. If no clear etiology for the lymphadenopathy is available, or if acute infectious mononucleosis occurs, discontinuation of Protopic® should be considered.

>

- Protopic® should not be used in patients with congenital or acquired immune deficiencies or in patients undergoing treatment which causes immunosuppression. Exposure of the skin to sunlight should be minimised, and use of ultraviolet (UV) light (sunbeds, treatment with UVB or PUVA) should be avoided. Consultancy on appropriate protection against sun should be provided during treatment with Protopic®.

In the beginning of May, relevant doctors received a letter informing them of the above important risk-reducing measures and recommendations in relation to treatment with Protopic®.

References:

1. *Hui RL, Lide W, Chan J, Schottinger J, Yoshinaga M, Millares M. Association between exposure to topical tacrolimus or pimecrolimus and cancers. Ann Pharmacother 2009 Dec; 43 (12): 1956-1963*
2. *Schneeweiss S, Doherty M, Zhu S, Funch D, Schlienger RG, Fernandez-Vidaurre C, Seeger JD. Topical treatments with pimecrolimus, tacrolimus and medium- to high-potency corticosteroids, and risk of lymphoma. Dermatology 2009; 219 (1): 7-21*
3. *Arana A, Wentworth CE, Fernadez-Vidaurre C, Schlienger RG, Conde E. Lymphoma among patients with atopic dermatitis treated with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCIs). Presented at the annual meeting of the International Society for Pharmacoepidemiology. Brighton, UK 2010.*

Indication for Protopic® 0.1% and 0.03%:
Protopic® 0.1% ointment is indicated for adults and adolescents (16 years and above), whereas Protopic® 0.03% ointment is indicated for adults, adolescents and children from the age of 2.

Protopic® 0.1% as well as Protopic® 0.03% are licensed for:

Treatment of eczema
Adults and adolescents (16 years and above)
Treatment of moderate to severe atopic dermatitis in adults who do not respond satisfactorily or are intolerant to conventional treatments such as topical corticosteroids.

Maintenance treatment
Treatment of moderate to severe atopic dermatitis in order to prevent eczema and to extend intervals without disease in patients who experience frequent illness exacerbations (i.e. occurring four times or more per year), and who have had an initial response to a maximum of 6 weeks of treatment with tacrolimus ointment twice daily (lesions healed, almost healed or only mildly affected).

Only **Protopic® 0.03%** is approved for the treatment of children:
Children (2 years and above)
Treatment of moderate to severe atopic dermatitis in children who have not responded satisfactorily to conventional treatments such as topical corticosteroids.

Risk of blood clots associated with hormonal contraceptives

A new major Danish registry study has investigated the risk of blood clots in women using different types of hormonal contraceptives. The study concludes, among other things, that women using vaginal rings (NuvaRing®) and contraceptive patches (Evra®) have the highest risk of blood clots.

You can read more about this at our website: *Risk of blood clots associated with hormonal contraceptives*.

Based on this study, the Danish Health and Medicines Authority will raise the issue in the EU Pharmacovigilance Working Party to discuss whether further and stricter measures are required in the product information for the medicine.

Focus on consumption development, adverse reactions reported, age and dose recommendations in relation to Pradaxa®

In March, in collaboration with the Thrombosis Centre in Aalborg, the Danish Health and Medicines Authority published an evaluation of all adverse reaction reports in Danish Pharmacovigilance Update for the period 22 August 2011 up to and including 23 February 2012 in connection with a new indication (prevention of apoplexy in patients with non-valvular atrial fibrillation) for Pradaxa® (dabigatran etexilate).

We now once more focus on consumption development, adverse reactions reported, age and dose recommendations in relation to Pradaxa®. You can read more about this at our website: *Pradaxa – consider age and follow dose recommendations*.

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