1.1. Metoject® and device-related problems

Introduction

On the 17th of March 2010 the Dutch Health Care Inspectorate (IGZ) reported that for patients receiving methotrexate injections, the registered drug Metoject® [1] should be used in stead of preparation of methotrexate injections in the pharmacy [2]. Preparation of methotrexate injections in the pharmacy in similar strengths to the Metoject® injections would no longer be reimbursed [2,3].
Metoject® was granted marketing authorization in the Netherlands in 2003 and is indicated for the treatment of *severe active rheumatoid arthritis in adults*, *polyarthritic severe, juvenile idiopathic arthritis that does not adequately respond to treatment with NSAID's* and *severe and generalized psoriasis vulgaris and arthritis psoriatica in adult patients who do not respond to conventional therapies* [1].
On the 10th of August 2010, the Netherlands Pharmacovigilance Centre Lareb sent a letter to the Dutch Medicines Evaluation Board (MEB) to inform the MEB about an increase in reports of device complications for this specific brand of methotrexate injections. After this letter was sent, Lareb received an additional four reports about device complications associated with Metoject® injections. Although device complications are not typically a subject for a quarterly report, the number and nature of these reports was reason for Lareb to include this 'signal'.

Reports

In total the Netherlands Pharmacovigilance Centre Lareb received 39 reports in association with the use of Metoject®. Twenty-four of these reports were received after 17 March 2010. Ten of these twenty-four reports were about similar device complications. Before 17-03-2010 Lareb had only received one report about a device complication in association with the use of Metoject®. This was a report from 09-03-2006 where a pharmacist reported that the patient had to use more methotrexate because fluid leaked out of the injection site and an injection site reaction with pain occurred. No reports about device complications for other methotrexate injections were received. The ten recent reports about medical device complication in association with Metoject® are described below.

Table 1. Reports of device complications associated with the use of Metoject®

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 109200 F, 61 – 70 years	Metoject injection 50mg/ml 0.2ml osteoporosis	not reported	device complication	minute no change unknown
B 108792 F, 31 – 40 years	Metoject injection 50mg/ml 0.5ml rheumatoid arthritis	not reported	device complication, mouth ulceration, reaction after drug substitution	1 day dose reduction not recovered
C 108519 F, unknown	Metoject 20 injection 10mg/ml 2ml rheumatoid arthritis	folic acid	device complication, reaction after drug substitution	not reported discontinued not reported
D 108339 F, unknown	Metoject 15 injection 10mg/ml 1.5ml	not reported	device complication	not reported unknown unknown
E 107529 F, 41 – 50 years	Metoject injection 50mg/ml 0.4ml rheumatoid arthritis	not reported	device complication, reaction after drug substitution	not reported not applicable not reported

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
F 107262 F, 51 – 60 years	Metoject 15 injection 10mg/ml 1.5ml rheumatoid arthritis	not reported	device complication, reaction after drug substitution	2 year after first start of methotrexate injections not applicable not yet recovered
G 111954 F, 51 – 60 years	Metoject injection 50mg/ml 0.3ml rheumatoid arthritis	not reported	device complication	3 week not applicable not recovered
H 110217 M, 51 – 60 years	Metoject 25 injection 10mg/ml 2.5ml spondyloarthropathy	folic acid	device complication, reaction after drug substitution	
I 110209 M, 41 – 50 years	Metoject 15 injection 10mg/ml 1.5ml psoriatic arthritis		device complication, reaction after drug substitution	1 minute no change not recovered
J 110083 F, 41 – 50 years	Metoject injection 50mg/ml 0.5ml rheumatoid arthritis		device complication, stomatitis, reaction after drug substitution, fatigue, infection aggravated	1 month no change not recovered

Patient A (a consumer report) reported bluntness of the injection needles, the syringe itself being very fragile, breaking easily and the patient could not open the safety cap on the injection due to rheumatism in his hands.

Patient B (a consumer report) used methotrexate (unknown brand) for five years without problems before he was switched to methotrexate from the brand Metoject®. He suffered from painful, bleeding mouth ulceration and the dose of Metoject® was reduced. The patient also reported that the needles of the Metoject® injections are blunt and difficult to replace.

Patient C (a consumer report) reported that the needle of the Metoject® injections is blunt and this has caused skin problems and pain. The needle is too thick and not removable from the syringe. The patient cannot remove the safety cap from the injection due to rheumatism in her hands. The patient had used magisterial preparations of methotrexate injections in the past without problems.

In Patient D (a pharmacist report) bluntness of the needles on the Metoject® injections is reported.

Patient E (a consumer report) reported bluntness of the needles on the Metoject® injections. The patient has to press the needles through the skin, which is painful. During previous methotrexate use, the injections were painless.

Patient F (a consumer report) reported that the injection needles of Metoject® are blunt, and the patient cannot open the safety cap on the injection due to rheumatism in her hands. Prior use of methotrexate injections did not cause any problems.

Patient G (a consumer report) reported bluntness of the injection needles of Metoject® which leads to a burning sensation at the injection site.

In Patient H (a physician report) bluntness of the Metoject® needles is reported. Prior use of methotrexate injections prepared in the hospital pharmacy did not cause any problems. This physician has treated multiple patients with similar problems.

Patient I (a consumer report) reported that the injection needles of Metoject® are blunt, and the patient cannot easily open the safety cap on the injection without pricking his own fingers. The needles cap causes a vacuum in the needle, causing fluid to leak out of the needle once the cap has been removed. The needles cannot be removed from the syringe. The liquid level in the syringe itself is obscured by a large sticker. The packaging of the product the patient received was in Scandinavian. Prior use of methotrexate injections did not cause any problems.

Patient J (a consumer report) reported stomatitis, fatigue, aggravation of infections and bluntness of the Metoject® needles. Prior use of methotrexate injections did not cause any problems.

Other sources of information

Literature
To the best of our knowledge there are no publications about device problems associated with the use of Metoject®.
On the website of The Dutch Institute for Rational Use of Medicine (IVM) [4], several additional cases can be found of patients who report device problems with their Metoject® injections.

Databases
On November 24 2010, the association between medical device complications in association with the use of methotrexate (Metoject®) injections was disproportionally present in the Lareb database. The reporting odds ratio (ROR) based on 10 reports was 96.2 (95% CI 48.4- 191.5)
On January 11 2011, the database World Health Organization (WHO) contained 8 reports of device complications (Higher Lever term in MedDRA) in association with the use of the brand Metoject®. All these cases originated from the Netherlands. Due to a backlog in the WHO database not all the Lareb cases will have been incorporated in the WHO database yet.

On December 2nd 2010, the Eudravigilance database contained no reports of the MedDRA Higher Level Terms “Device issues” and “Complications associated with device” in association with the use of Metoject®.

Prescription data
The College for health insurances’ GIP database [5] gives the number of methotrexate users in the Netherlands in 2009, namely 55,764. However the route of administration and the brand of medication which was used are not specified by the GIP database.

Discussion and Conclusion
Spontaneous ADR reporting can be influenced in different ways by external events. Among other factors, changes in drug tenders or reimbursements can lead to more reporting about certain (brands of) drugs [6]. The fact that pharmacy preparations of methotrexate injections in similar strengths to the Metoject® injections will no longer be reimbursed [2,3] is an important factor when investigating the reports of device complications associated with Metoject®. However, there is a lot of similarity between the problems that were reported with these injections (bluntness of needles and more injection site pain). It should be considered to further investigate if device complications are an issue for the Metoject® injections.

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References
1. Dutch SmPC Metoject® 10 mg, oplossing voor injectie in voorgevulde injectiespuit 10 mg/1 ml. (version date: 24-7-2003, access date: 18-11-2010) http://db.cbg-meb.nl/IB-teksten/h28236.pdf.
2. The Health Care Inspectorate (IGZ). Standpunt VWS en IGZ inzake methotrexaat-injectiespuiten per 17 maart 2010. (version date: 17-3-2010, access date: 18-11-2010) http://www.igz.nl/onderwerpen/geneesmiddelen-en-medische-technologie/geneesmiddelen/standpunt_methotrexaatinjectiespuiten/.
3. De Leeuw M. Chaos bij vergoeding Metoject. Pharm Weekbld 2010;(14):6-7.
4. The Dutch Institute for Rational Use of Medicine (IVM). Website Instituut voor Verantwoord Medicijngebruik (IVM). (version date: 18-11-2010, access date: 18-11-2010) http://www.medicijngebruik.nl/.
5. College for Health Insurances. GIP database. (version date: 9-6-2009, access date: 10-2-2010) http://www.gipdatabank.nl/index.asp?scherm=tabellenFrameSet&infoType=g&tabel=01-basis&item=J01FF.
6. Motola D, Vargiu A, Leone R, Conforti A, Moretti U, Vaccheri A, Velo G, Montanaro N. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. Drug Saf 2008;31(7):609-16.

This signal has been raised on April 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).