

## 1.1. Angioedema and allergic reactions in metoclopramide containing products

### Introduction

Metoclopramide (Primperan<sup>®</sup>, Migrafin (combination with lysine acetylsalicylate) is a phenothiazide anti-emetic which has been marketed in the Netherlands since December 1968. It is registered for use in nausea. The metoclopramide lysin acetylsalicylate is marketed for use in migraine. Common adverse reactions include somnolence, and gastrointestinal effects such as diarrhoea and constipation.

In some preparations the possibility of an immunologically mediated reaction, including anaphylaxis is mentioned explicitly.

### Reports

On December 1 2008, the Netherlands Pharmacovigilance Centre Lareb has received three reports of angioedema related to the use of metoclopramide (Primperan<sup>®</sup>). Metoclopramide was in all cases considered as the only suspect medication. In two cases (A and C) the reaction resolved after withdrawal, however in at least one report (case A) the reaction necessitated antihistamine treatment. In case B a relation with metoclopramide is supported by a latency of two hours. However ongoing use of metoclopramide was reported in this case. In one case hospital admission due to the reaction was necessary. In an additional case angioedema possibly led to prolongation of stay in hospital. In none of the three cases evidence for other non-immunological reactions was highlighted. Characteristics are shown in table 1, reports of angioedema associated to metoclopramide use.

Besides these three reports, Lareb received three additional cases of facial oedema, which may be a feature of angioedema. Of periorbital oedema which is a more specific feature of angioedema Lareb did not receive any reports in relation to metoclopramide use. Lareb received several reports of potential hypersensitivity reactions to metoclopramide including two reports of anaphylaxis.

Table 1: Reports of angioedema associated to metoclopramide use.

Patient, Number, Sex, Age	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 41523 F,	metoclopramide 20mg nausea	gabapentin 600mg	angioedema	7 hour discontinued recovered
B 43942 F, 16	metoclopramide 10mg nausea	amoxicillin clavulanate suspension prednisone 5mg	angioedema dystonia, drowsiness,	2 hour no change recovered
C 75902 F, 63	metoclopramide tablet 10mg nausea	omeprazole 40mg, hydrochlorothiazide 25mg	angioedema	2 day discontinued recovered

### SmPCs

In none of the Dutch SmPCs of mono preparations containing metoclopramide angioedema is mentioned explicitly [1-7]. The SmPCs of Primperan and Pharmachemie, Accord and Ratiopharm metoclopramide preparations mention "allergic reaction including anaphylaxis" [1-3,6]. The SmPCs of Actavis and Centrafarm metoclopramide products do not mention any allergic reactions [4,5]. The SmPC of Migrafin (lysine acetylsalicylate/metoclopramide) mentions angioedema only for the first component [7].

## Literature

Hypersensitivity reactions to metoclopramide are well described in literature, including one case report of anaphylaxis [8].

## Conclusion

Angioedema should be mentioned explicitly in the SmPCs of all metoclopramide preparations. Furthermore in SmPCs lacking information on allergic reactions to metoclopramide, the possibility of occurrence of these reactions should be addressed.

## References

1. Dutch SmPC Primperan<sup>®</sup>. (version date: 30-1-2008, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h05250.pdf>.
2. Dutch SmPC metoclopramide HCl Pharmachemie. (version date: 23-2-2007, access date: 1-12-0008) <http://db.cbg-meb.nl/IB-teksten/h18026.pdf>.
3. Dutch SmPC metoclopramide HCl Ratiopharm. (version date: 23-2-2007, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h09715.pdf>.
4. Dutch SmPC metoclopramide HCl Actavis. (version date: 26-1-2007, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h55926.pdf>.
5. Dutch SmPC metoclopramide HCl Centrafarm. (version date: 26-1-2007, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h55926.pdf>.
6. Dutch SmPC metoclopramide HCl Accord. (version date: 1-11-2007, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h11811.pdf>.
7. Dutch SmPC Migratin<sup>®</sup>. (version date: 24-4-2008, access date: 1-12-2008) <http://db.cbg-meb.nl/IB-teksten/h18026.pdf>.
8. Kerstan A, Seitz CS, Brocker EB, Trautmann A. Anaphylaxis during treatment of nausea and vomiting: IgE-mediated metoclopramide allergy. *Ann Pharmacother* 2006;40(10):1889-90.

*This signal has been raised on February 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbg-meb.nl/cbg/en/default.htm](http://www.cbg-meb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*