

Metronidazole gel Metrosa® and product quality issue of flaking of the gel

Introduction

Metronidazole gel Metrosa® is indicated for *the topical treatment of acne rosacea*.

Metronidazole is a 5-nitro-imidazol-derivate, with activity against anaerobic protozoa and bacteria, probably due to an interference with DNA by a metabolite of metronidazole. The exact mechanism of action in acne rosacea is unknown. One of the mechanisms of action might be anti-oxidizing activity resulting in anti-inflammatory effects.

Metronidazol gel Metrosa® was granted marketing authorization in the Netherlands in 2006 [1].

Rosacea is a common chronic inflammatory dermatosis. The exact pathophysiology is unknown, but most likely is has a multifactorial etiology with a genetic preposition, where microbes, ultraviolet (UV) radiation, nutrition, extremes of temperatures, (skin) barrier disruption, psychosocial stress, and hormonal influences may play a role [2-6].

Report

From 6 June 2017 to 8 March 2018 the Netherlands Pharmacovigilance Centre Lareb received three reports of a product quality issue with the use of metronidazole, all concerning metronidazole gel Metrosa® and flaking of the gel.

Report 259711

This non-serious spontaneous report from a consumer concerns a woman aged 41-50 years, with skin discomfort (a tense feeling of the skin) and product quality issue (flaking of the dried up gel with the result that the gel does not remain on the skin), following administration of metronidazole gel with the brand name Metrosa®, for rosacea with a latency of 10 minutes after application. Metronidazole Metrosa® was withdrawn and metronidazole cream with the brand name Rosiced® was started. Hereafter, the patient did no longer experience the skin discomfort and the flaking of the gel.

Report 243838

This non-serious spontaneous report from a consumer concerns a woman aged 61-70 years, with lack of drug effect (no effect on redness and burning feeling) and pharmaceutical product complaint (it forms sheets that you can rub off when you apply a day cream), following substitution of metronidazole gel with the brand name Rozex®, to metronidazole gel with the brand name Metrosa®, for rosacea with a latency of minutes after start. The dose for metronidazole Metrosa® is not changed. The patient still experienced the reactions at the time of reporting. Concomitant medication was not reported. The past drug therapy indicates that the patient used metronidazol gel with the brand name Rozex® without similar complaints.

Report 240878

This non-serious spontaneous report from a consumer concerns a woman aged 61-70 years, with product quality issue following topical administration of metronidazole gel with the brand name Metrosa®, for rosacea. The gel was peeling from the skin, also when applied very thinly. The dose for metronidazole was reduced. The patient still experienced the reaction at the time of reporting. Concomitant medication was not reported. The past drug therapy indicates that the patient had metronidazole gel with the brand name Rozex® without similar complaints.

Other sources of information

SmPC

The Dutch SmPC of metronidazol gel Metrosa® reports the following excipients: Phenoxyethanol, propylene glycole, hypromellose and purified water [1].

The Dutch SmPC of metronidazol gel Rozex® reports the following excipients: Propylene glycol, carbomer, methylparahydroxybenzoate, natriumedetate, propylparahydroxybenzoate, natriumhydroxide and purified water [7].

Literature

No scientific literature was found concerning the association metronidazole gel and product quality issue.

Database

Table 1. Reports of the PT “product quality issue” associated with metronidazole in the Lareb database [8].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Product quality issue	3	0.41 (0.13 – 1.29)*

*The ROR was calculated for all metronidazole products excluding combination preparations

For the Eudravigilance and WHO databases, the ROR’s were not added, because the PT Product quality issue can comprise many kinds of different issues.

Prescription data

Table 2. Number of patients using metronidazole with ATC D06BX01 (this ATC concerns metronidazole gels and creams) in the Netherlands [9].

Drug	2012	2013	2014	2015	2016
Metronidazol with ATC D06BX01	91,003	90,779	94,558	93,892	94,231

Mechanism

As possible mechanism, the flaking of the metronidazole gel Metrosoa® and not of the metronidazole gel Rozex®, might be caused by a difference concerning the excipients. The excipients are reported above in the paragraph “SmPC”. Possibly the absence of carbomer or the presence of phenoxyethanol in Metrosoa® may play a role. Furthermore, possible differences in the quantities of the different excipients may be of influence.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three report from patients who experienced a similar reaction of flaking of metronidazole Metrosoa® gel. Two of these reporters mentioned that they did not experience this reaction during previous use of metronidazole gel Rozex®. Besides inconvenience, the gel peeling from the skin may possibly result in ineffectiveness of the drug. Possibly a difference between the excipients of the products might play a role in the flaking. Maybe specific individual skin properties like a dry skin compared to a more oily skin, may increase the risk of flaking of the gel.

Based on the reports received by Lareb, it is suggested that flaking of Metrosoa® might occur more easily compared to Rozex®.

References

1. Dutch SmPC metronidazol Metrosoa® 7,5 mg/g gel. (version date: 18-06-2015, access date: 8-3-2018). <https://db.cbg-meb.nl/IB-teksten/h33518.pdf>.
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4. Elewski BE, Draeos Z, Dreno B, Jansen T, Layton A, Picardo M. Rosacea – global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol.* 2011;25:188-200.
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6. Del Rosso JQ, Gallo RL, Tanghetti E, Webster G, Thiboutot D. An evaluation of potential correlations between pathophysiologic mechanisms, clinical manifestations, and management of rosacea. *Cutis*. 2013;91:1-8.
7. Dutch SmPC metronidazol Rozex® 7,5 mg/g gel. (version date: 01-03-2017, access date: 8-3-2018). <https://db.cbq-meb.nl/IB-teksten/h14416.pdf>.
8. Lareb database. (version date: 2018, access date: 08-03-2018) <https://www.lareb.nl/nl/databank/>.
9. College for Health Insurances. GIP database. (version date: 2018, access date: 08-03-2018) <http://www.gipdatabank.nl/>.

This signal has been raised on May 9, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl