

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

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).

In 2018 Lareb informed the Dutch Medicines Evaluation Board (MEB) about the first three cases of a product quality issue related to Metronidazole gel Metrosa® (7). Since then 14 more cases have been received and this was the reason to provide an update of the signal.

Reports

In the period from June 6th 2017 to February 11th 2021 the Netherlands Pharmacovigilance Centre Lareb received 17 reports of a product quality issue with the use of metronidazole, all concerning metronidazole gel Metrosa® and flaking of the gel.

No	ID, sex, age, primary source	Drug	Dosage	Indication	Reported ADRs	Latency after start, Action taken, Outcome
1	NL-LRB-240878, female, 60-70 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	2 applications / 1 Days	Rosacea	Product quality issue <i>The gel was peeling from the skin, also when applied very thinly. The dose for metronidazole was reduced. The past drug therapy indicates that the patient had metronidazole gel with the brand name Rozex® without similar complaints.</i>	- Dose Reduced Not Recovered
2	NL-LRB-00259711, female, 40-50 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Skin discomfort, Product quality issue <i>Tense feeling of the skin and flaking of the dried up gel with the result that the gel does not remain on the skin; because of this the drug is not/barely effective.</i> <i>Metronidazole Metrosa® was withdrawn and metronidazole cream with the brand name Rosiced® was started.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.</i>	10 Minutes Drug Withdrawn Recovered, Recovered

3	NL-LRB-243838, female, 60-70 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application /	Rosacea	Lack of drug effect, Pharmaceutical product complaint, Therapeutic response unexpected with drug substitution <i>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®. The past drug therapy indicates that the patient used metronidazol gel with the brand name Rozex® without similar complaints</i>	- Dose Not Changed Not recovered
4	NL-LRB-00313214, male, 40-50 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 1 Days	Rosacea	Product quality issue <i>Flaking of the dried gel on the skin. In the morning my face if covered in flakes. It striked me that the tube was not sealed, even though the lid has a "spike" to open a seal.</i> <i>The patient used metronidazole gel of brand Rozex® in the past, without this product issue.</i>	4 Hours Dose Not Changed Not Recovered
5	NL-LRB-00331664, female, 40-50 years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Desquamation, Product quality issue <i>Large number of flakes on the face, every time moments after application. Unclear if the product itself flakes or whether it affects the skin.</i>	10 Minutes Drug Withdrawn Not Recovered, Not Recovered
6	NL-LRB-00337334, female, 30-40 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G Levothyroxine	1 application / 12 Hours	Rosacea	Product quality issue, Skin tightness <i>Gel flakes after application and skin feels tense.</i>	15 Minutes Dose Not Changed Not Recovered, Not Recovered
7	NL-LRB-00336175, female, 30-40 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue <i>When the gel dries it flakes. Need to wash the face with water to clean it.</i>	30 Minutes Dose Not Changed Not Recovered
8	NL-LRB-00342595, male, 20-30 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue <i>Flaking of the gel</i>	20 Minutes Drug Withdrawn Unknown
9	NL-NOVPHSZ- PHHY2019NL168249, female, age unknown, Other health professional ----- Consumer or other non health professional	Metrosa Gel 7,5Mg/G	/ 1 Days	Rosacea	Desquamation, Product quality issue	- Drug Withdrawn Not Recovered, Not Recovered
10	NL-LRB-00361166, male, 60-70 Years, Consumer or other	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue,	30 Minutes Drug Withdrawn Recovered

	non health professional				Therapeutic response unexpected with drug substitution <i>After the gel dries it is flaking, as if the patient's skin is peeling. Past drug therapy : metronidazol gel 7,5mg/g (brand Metrosa®) with product quality issue (also flaking of the gel after drying), metronidazol gel 7,5mg/g (brand Rozex®) with no adverse event.</i>	
11	NL-LRB-00372638, female, 20-30 years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue <i>Soon after application of the gel the gel is flaking.</i>	15 Minutes Not Applicable Not Recovered
12	NL-LRB-00373200, female, 40-50 years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Therapeutic response unexpected with drug substitution, Product quality issue <i>Flaking after application. Reaction occurred after switch from Rozex® to Metrosa®.</i>	- 5 Minutes Not Applicable Unknown, Not Recovered
13	NL-LRB-00374248, female, 50-60 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application /	Rosacea	Therapeutic response unexpected with drug substitution, Application site dryness, Product quality complaint <i>Flaking after the gel dries. Reaction occurred after switch from Rozex® to Metrosa®.</i>	- Not Applicable Not Recovered
14	NL-LRB-00383252, female, 40-50 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue <i>Every time after application the gel dries and flakes on the skin.</i>	1 Hours Not Applicable Not Recovered
15	NL-LRB-00395292, female, 50-60 years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	2 applications / 1 Days	Rosacea	Product quality issue <i>About 2 hours after application the gel changes in thin flakes.</i>	2 Hours Dose Not Changed Not Recovered
16	NL-LRB-00397483, female, 30-40 Years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 12 Hours	Rosacea	Product quality issue <i>Flaking on the skin after application.</i>	- Not Applicable Not Recovered
17	NL-LRB-00413028, female, 20-30 years, Consumer or other non health professional	Metrosa Gel 7,5Mg/G	1 application / 1 Days	Rosacea	Product quality issue <i>After application of the gel. dry (white) flakes are formed that detach from the skin.</i>	15 Seconds Drug Withdrawn Not Recovered

Flaking of the product occurred after drug substitution from metronidazole Rozex® into metronidazole Metrosa® in 6 cases (case 1, 3, 4, 10, 12, 13).

Four additional reports of consumers all using metronidazole gel 7.5 mg/g (Metrosa®) describing the same flaking of the gel that were not reported to Lareb were found at www.meldpuntmedicijnen.nl and www.mijnmedicijn.nl. Of these reports two reactions occurred after drug substitution from metronidazole (Rozex®) and metronidazole cream into metronidazole gel (Metrosa®). The third reporter described that the reaction resolved after substitution of metronidazole (Metrosa®) into metronidazole cream (Rosiced®). Three out of these four users doubt the efficacy of the gel.

	Primary source	Drug	Reported ADR	Substitution	Source
18	Consumer	Metrosa gel 7,5mg/g,gel Metronidazol	<i>After application of the gel, a film layer is formed on the skin which is completely dried and bursts open after half an hour. Then, my face is covered with flakes. Beside the fact that I cannot show my face anywhere like this, I wonder if this product is effective as it does not remain on the skin.</i>		Meldpuntmedicijnen.nl
19	Consumer	Metrosa gel 7,5MG/G	<i>The cream contains more metronidazole. I prefer application of the cream. The Metrosa gel starts to flake, which looks awful. I would like to return to using the cream.</i>	<i>Was prescribed Metrosa gel instead of cream.</i>	Meldpuntmedicijnen.nl
20	Consumer	Metrosa gel 7,5MG/G	<i>It is not absorbed by the skin and it is flaking all day!</i>	<i>Works very differently from Rozex!</i>	Meldpuntmedicijnen.nl
21	Consumer, female 40-50	Metronidazol 7,5MG/G, Rosacea	<i>Gel was so flaky after it dried that it was barely effective. It was more like a peel off mask than a medicine. In no time the gel detached from the skin. It had little positive effect.</i>	<i>Switched to metronidazol (Rosiced®) cream which is absorbed well through the skin and is effective.</i>	Mijnmedicijn.nl

4 reporters mentioned that they were doubting the effectiveness of the metronidazole (Metrosa®) gel because of the flaking. These 4 reporters include 2 Lareb cases (2 and 3) and 2 reports from meldpuntmedicijnen.nl/ mijnmedicijn.nl (cases 18 and 21)

Other sources of information

SmPC

In the SmPC it is stated that a thin layer of film gel should be applied twice a day on the affected sites. The chance of flaking of the gel is not described in the SmPC.

The Dutch SmPC of metronidazol gel Metrosa® reports the following excipients: Phenoxyethanol, propylene glycol, hypromellose and purified water (1).

The Dutch SmPC of metronidazol gel Rozex® reports the following excipients: Propylene glycol, carbomer, methylparahydroxybenzoate, sodium edetate, propylparahydroxybenzoate, sodiumhydroxide and purified water (8).

Literature

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

Prescription data

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

Drug	2015	2016	2017	2018	2019
D06BX01 Metronidazol*	95,289	94,057	89,953	86,436	87,199

*The numbers in the GIP database include all metronidazole brands. Therefore, we cannot use these numbers to determine how many patients switched from Rozex® to Metrosa®.

Mechanism

The flaking of the metronidazole gel Metrosa® and not of the metronidazole gel Rozex® can most likely be explained by the difference in viscosity enhancers used. The excipients are reported above in the paragraph "SmPC". Metrosa® contains the viscosity enhancer hypromellose while Rozex contains carbomer. Hypromellose is a cellulose derivative. Cellulose derivatives create a film layer (also called xerogel) when water evaporates and the gel dries on the skin. This layer can become flaky and therefore patients may prefer gels prepared with carbomer (10). It is unknown whether flaking of the gel influences the efficacy.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 17 reports from patients who experienced a similar reaction of flaking of metronidazole Metrosa® gel. Six of these reporters mentioned that they did not experience this reaction during previous use of metronidazole gel Rozex®. The flaking of the metronidazole Metrosa® gel and not of metronidazole Rozex® can be explained by the different viscosity enhancers used for preparation. Preparation of metronidazole Metrosa® is based on hypromellose while Rozex® is based on carbomer. Based on the reports received by Lareb and based on knowledge about viscosity enhancers, flaking of Metrosa® might occur more easily compared to Rozex®. Besides inconvenience, there are doubts that the gel peeling from the skin may possibly result in ineffectiveness of the drug, which could lead to non-compliance by patients.

References

1. Dutch SmPC metronidazol Metrosa® 7,5 mg/g gel [23-03-2021]. Available from: <https://db.cbg-meb.nl/IB-teksten/h33518.pdf>.
2. Rainer BM, Kang S, Chien AL. Rosacea: Epidemiology, pathogenesis, and treatment. *Dermatoendocrinol.* 2017;9(1):e1361574.
3. Steinhoff M, Schaubert J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. *J Am Acad Dermatol.* 2013;69(6 Suppl 1):S15-26.
4. Elewski BE, Draelos Z, Dréno 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(2):188-200.
5. Steinhoff M, Buddenkotte J, Aubert J, Sulk M, Novak P, Schwab VD, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc.* 2011;15(1):2-11.
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(3 Suppl):1-8.
7. Signals_2018_Metronidazol Metrosa and product quality issue.pdf.
8. Dutch SmPC metronidazol Rozex® 7,5 mg/g gel [23-03-2021]. Available from: <https://db.cbg-meb.nl/IB-teksten/h14416.pdf>.
9. College for Health Insurances. GIP database. [23-03-2021]. Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=gebr&spec=&item=D06BX01.
10. Receptteerkunde. Fifth ed. p. 784.

This signal has been raised on June 9, 2021. 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.cbg-meb.nl