

Clotrimazole and vaginal haemorrhage

Introduction

Vaginal clotrimazole (Canesten Gyno®) is indicated for *vulvovaginal infections with Candida species*, and available as cream with applicators (dose 5 gram; strengths 10 mg/g, 20 mg/g and 100 mg/g) and as vaginal capsule (500 mg) or vaginal tablet (200 mg and 500 mg). There are three different treatment regimens:

- 1) Canesten Gyno 1®, over-the-counter (OTC) available as 500 mg tablet and capsule or 100 mg/g cream, as a single dose treatment;
- 2) Canesten Gyno 3®, available as 200 mg tablet or 20 mg/g cream for 3 days (prescription only);
- 3) Canesten Gyno®, OTC available as 10 mg/g cream for 6 days [1-6].

Vaginal clotrimazole was granted marketing authorization in the Netherlands in 1976 [1].

The imidazole clotrimazole has a broad spectrum of fungistatic activity against skin infections with yeasts and moulds by inhibiting ergosterol synthesis. Since ergosterol is the main component of fungal cell membranes, membrane permeability is altered and essential cell structures are lost. About 3 to 10% of vaginally applied dose is systemically absorbed [1-6].

Causes for abnormal vaginal haemorrhage, other than normal menstrual bleedings, differ between the reproductive- and postmenopausal phase. In the reproductive phase, menorrhagia may occur due to myoma, IUD and with anticoagulant therapy. Irregular or intermenstrual bleeding can occur spontaneously, or can be caused by early pregnancy, break-through bleedings with hormonal contraceptives and disorders of the perineum, vagina and cervix.

Postmenopausal causes of vaginal haemorrhage are endometrial abnormalities, vaginal atrophy and the use of tamoxifen or hormonal therapy. In addition, in both phases bleedings caused by infections (e.g. chlamydia) and contact bleedings can occur [7].

Reports

From 2006 until January 6th, 2020, The Netherlands Pharmacovigilance Centre Lareb received 42 reports of vaginal haemorrhage, metrorrhagia, menorrhagia and bloody vaginal discharge with the use of vaginal clotrimazole products. The complete table is shown in Appendix I.

Demographics

The majority of 38 reports were reported by consumers and four were reported by pharmacists or physicians. Lareb received 13 reports via Marketing Authorisation Holders (MAH).

In 54% of the reports, the age of women 30 years or younger, reflecting the occurrence of vaginal mycosis in this age group [8].

Administration form

The administration forms in the reports differ, with vaginal cream in 18 reports, vaginal tablet in 15 reports and vaginal capsule in eight reports, leaving one report with an unknown clotrimazole product.

Type of bleeding

Type and severity of vaginal bleeding varies from 'pink or bloody discharge' in 11 reports, 'mild bleeding' in 11 reports, 'menstruation like bleeding' in six reports, 'worse than menstrual bleeding' in one report; leaving 13 reports with unspecified bleeding severity.

Timing

Time to onset of vaginal bleeding with clotrimazole varied from 'directly after insertion' in three reports to four days in another three reports, with a mode of two days (14 reports).

Eleven women recovered spontaneously in two to five days. In other reports women had not recovered at time of reporting or the outcome was unknown. Two patients consulted a general practitioner or gynaecologist for further investigation, which did not reveal another cause. In 7 reports, recurrence of vaginal bleeding with repeated use of clotrimazole has been mentioned.

Other explanations

Eight women mentioned the concomitant use of an oral contraceptive and two had an Intra Uterine Device (IUD). Three of these women specifically mentioned the bleeding pattern differed from

normal withdrawal bleeding or did not experience breakthrough bleeding before. One woman was pregnant and one was breastfeeding. Two women reported to have small wounds in labia and/or vaginal mucosa of unknown cause. Only four patients had concurrent complaints of vaginal irritation or pain.

Other sources of information

SmPC

The Dutch product information (SmPC) of Canesten Gyno 1[®] (tablet 500 mg, capsule 500 mg, cream 100 mg/g) and Canesten Gyno[®] (cream 10 mg/g) mention that clotrimazole cannot be used if infection related complaints are accompanied with symptoms of abnormal bleeding.

Canesten Gyno 3[®] (tablet 200 mg, cream 20 mg/g) product information mentions that application during the menstrual period may reduce efficacy of treatment.

Vaginal tablets need moisture for complete dissolution. Non-dissolved particles can be excreted from the vagina [1-6].

The UK SmPC of vaginal clotrimazole mentions vaginal haemorrhage as adverse drug reaction [9]. The Dutch SmPC of vaginal clotrimazole does not mention vaginal haemorrhage, contrary to the Dutch SmPC of vaginal miconazole [10].

Literature

In literature, no case-reports or studies were found that describe vaginal clotrimazole induced vaginal haemorrhage.

Databases

Table 1: Reports in Lareb, Eudravigilance (EV) and WHO VigiBase[®] databases regarding clotrimazole and vaginal haemorrhages [11].

	Drug	ATC	PT	N	ROR [95%CI]
Lareb	Clotrimazole	D01AC01	Vaginal haemorrhage*	1	n.a.
		G01AF02	Vaginal haemorrhage	28	132.74 [87.07 – 202.37]
			Genital haemorrhage	2	n.a.
			Metrorrhagia	2	n.a.
			Menorrhagia	1	n.a.
			Vaginal discharge (bloody)**	8	n.a.
WHO	Clotrimazole	G01AF02/ D01AC01***	Vaginal haemorrhage	438	45.4 [41.1-49.7]
			Genital haemorrhage	16	5.8 [3.6-8.0]
			Metrorrhagia	66	7.7 [6.0-9.4]
			Menorrhagia	10	1.6 [0.8-2.4]
			Vaginal discharge (bloody)**	n.a.	n.a.
EV	Clotrimazole	G01AF02	Vaginal haemorrhage	353	168.15 [168.15-190.34]
			Genital haemorrhage	14	6.51 [3.85-11.04]
			Metrorrhagia	11	7.62 [4.21-13.81]
			Menorrhagia	7	4.79 [2.28-10.08]
			Vaginal discharge (bloody)**	n.a.	n.a.

* Concerns an unknown topical clotrimazole product used for vaginal mycosis.

** Eight out of 22 reports of vaginal discharge concerned bloody discharge in Lareb database. In WHO and EV database, clinical information was not available.

*** In VigiBase[®], drugs are sorted with Active Ingredient, not split on ATC level.

Prescription data

Table 2: Prescription data of Canesten Gyno[®] from GIP databank; note that prescription data for OTC available Canesten Gyno 1[®] and Canesten Gyno 3[®] are not available [12].

		2014	2015	2016	2019	2018
G01AF02	Clotrimazol (Canesten gyno [®])	40,400	34,319	82,665	41,065	28,627

Mechanism

Local mechanical mucosal damage and azole drugs interacting with steroids, are two possible mechanisms for vaginal haemorrhage caused by vaginally applied azole drugs such as clotrimazole. With clotrimazole no relevant interactions are known, contrary to miconazole which can interact with coumarins by inhibiting cytochrome P450 2C9 resulting in increased bleeding tendency [13]. In our reports women had no known anticoagulant concomitant drugs. With the use of oral contraceptives (OCC), an increase of estrogen has been described via CYP 3A4 inhibition by systemic azoles and local miconazole. Menstruation irregularities and intermenstrual periods without the use of OCC have been mentioned as well [14]. For clotrimazole in particular, a drug interaction has not been described in literature before. Godamadunage et al. describe that all imidazole-containing azoles inhibit CYP 3A4, with clotrimazole being the least potent [15]. However, an increase in estrogen exposure does not explain menstrual irregularities as adverse drug reaction of azoles conclusively. Miconazole and clotrimazole also act on other enzymes and transporters that affect steroid hormone metabolism, such as P-glycoprotein 1 (Pgp), organic anion transporting polypeptide 2 (OATP), steroid and xenobiotic receptor (SXR), although clinical relevance is not clear yet [16].

Contact bleedings in general occur with chlamydial infections, endometritis and vaginal atrophy [7]. With vaginal mycosis, abnormal bleeding is not a common symptom [8], although vaginal mucosa can be hyperemic and assumed to be irritated easily by drug compounds of vaginally administered creams, suppositories and tablets. However, with mechanical damage, one would expect a more frequent notice of pain and irritation in the reports.

Discussion and conclusion

The occurrence of vaginal bleeding shortly after start of clotrimazole, the absence of previous blood loss along with the reported dechallenges and rechallenges, are supportive of a causal relationship with clotrimazole. Disproportionate reporting in Lareb, Eudravigilance and WHO database, as well as labelling information in UK SmPC support the association as well.

However, misdiagnosis by patients themselves of sexually transmitted disease (STD) like chlamydia infection, or vaginal atrophy cannot be ruled out. Also, vaginal bleeding can occur spontaneously. Since the reports show large variation in type of vaginal haemorrhage occurring with different administration forms, one clear explanation is lacking.

Women should be informed about the occurrence of vaginal haemorrhage with the use of clotrimazole in a similar way as with vaginal miconazole. Attention for this association is warranted, since vaginal bleeding may be indicative for additional vaginal or endometrial conditions.

References

1. Dutch SmPC Canesten® gyno crème. (version date 14-11-2011) https://www.geneesmiddeleninformatiebank.nl/smpc/h07856_smpc.pdf
2. Dutch SmPC Canesten® gyno tablet. (version date 12-3-2012) https://www.geneesmiddeleninformatiebank.nl/smpc/h06517_smpc.pdf
3. Dutch SmPC Canesten® gyno 1 crème. (version date 9-7-2015) https://www.geneesmiddeleninformatiebank.nl/smpc/h10972_smpc.pdf
4. Dutch SmPC Canesten® gyno 1 tablet. (version date 9-2015). https://www.geneesmiddeleninformatiebank.nl/smpc/h10051_smpc.pdf
5. Dutch SmPC Canesten® gyno 1 zachte capsule. (version date 14-8-2014) https://www.geneesmiddeleninformatiebank.nl/smpc/h114223_smpc.pdf
6. Dutch SmPC Canesten® gyno 3 crème, tablet. (version date 26-5-2000) https://www.geneesmiddeleninformatiebank.nl/smpc/h08935_smpc.pdf
7. Dutch NHG Standaard Vaginaal bloedverlies (M28). (version date 8-2014) <https://www.nhg.org/standaarden/volledig/nhg-standaard-vaginaal-bloedverlies>
8. Dutch NHG Standaard Fluor vaginalis (M38). (version date 5-2016) <https://www.nhg.org/standaarden/volledig/nhg-standaard-fluor-vaginalis>
9. UK SmPC Canesten 10% w/w Vaginal Cream. (version date 16-1-2018) <https://www.medicines.org.uk/emc/product/123/smpc>
10. Dutch SmPC Gyno-Daktarin®. (version date 9-12-2016) https://www.geneesmiddeleninformatiebank.nl/smpc/h10634_smpc.pdf
11. Vigibase®. WHO Global Individual Case Safety Reports database. (access date: 31-3-2020) <https://www.who-umc.org/vigibase/vigilyze/> (access restricted).
12. College voor Zorgverzekering. GIP Databank. (access date: 28-1-2020) <http://www.gipdatabank.nl/>.

13. Lansdorp, Bressers, Dekens-Konter. Potentiation of acenocoumarol during vaginal administration of miconazole. Br J Clin Pharmacol 1999 (44): 225-226. Via: https://databankws.lareb.nl/Downloads/bjcp1999_344.pdf
14. Baxter K, Preston CL (ed). Stockley's Drug Interactions (online). Combined hormonal contraceptives + Azoles. (version date 27-6-2017) London: The Pharmaceutical Press.
15. Godamudunage MP, Grech AM, Scott EE. Comparison of Antifungal Azole Interactions with Adult Cytochrome P450 3A4 versus Neonatal Cytochrome P450 3A7. Drug Metab Dispos. 2018 Sep;46(9):1329-1337
16. Drugbank. Clotrimazole, Miconazole. (access date 28-1-2020) <https://www.drugbank.ca/drugs/DB00257>

This signal has been raised on June 4, 2020. 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

Appendix I

Lareb reports, table, sorted by administration form; legend: **Cream**, **Tablet**, **Capsule**

No	ID, sex, age, primary source	Drug, dose	Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1	NL-LRB-59554, female 20-30 Years, Pharmacist	CANESTEN GYNO Creme 1 DF / 1 Day	Vaginal mycosis		Bleeding vaginal	1 Days	Drug Withdrawn	Recovered
3	NL-LRB-137065, female, 30-40 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 5 gram / 1 Day	Vaginal inflammation		Vaginal bleeding, Vaginal discomfort, Pruritus vulvae	4 Days 3 Days 3 Days	Dose Not Changed	Unknown, Unknown, Unknown
4	NL-LRB-151869, female, 40-50 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 1 DF/ 1 Day	Vaginal candidiasis		Vaginal bleeding	1 Days	Drug Withdrawn	Recovered
5	NL-BAYER-2013-044754, female, 20-30 Years, Consumer or other non health professional	Canesten Vaginal creme ? mg/g	Vaginal mycosis	Ethinylestradiol/ Levonorgestrel Tablet 30/150Ug	Vaginal bleeding, Itch, Adverse event NOS	1 Days 1 Days 1 Days		Recovered, Recovered, Recovered
6	NL-LRB-154661, female, 10-20 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 1 DF / 1 Day	Vaginal mycosis	Clindamycine Opl 10Mg/Ml (Hcl), Ethinylestradiol /Levonorgestrel Tablet 30/150Ug	Vaginal discharge, Vaginal bleeding	16 Hours 16 Hours	Dose Not Changed	Recovering, Recovering
8	NL-LRB-192233, female, 30-40 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators (1a) – 4 days later 1 dosage form / 1 dosage form /	Candida vaginal Candida vaginal	Gyno Daktarin Vaginalcapsule 400Mg (1a)	Bleeding vaginal, Drug interaction potentiation	4 days	Drug Withdrawn, Not Applicable	Recovered, Recovered
14	NL-LRB-227456, female, 40-50 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 1 DF / 1 Day	Vaginal mycosis	Levonorgestrel lud 52Mg	Vaginal haemorrhage	1 Days	Dose Not Changed	Not Recovered
15	NL-LRB-234674, female, 30-40 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 1 DF/	Vaginal mycosis		Vaginal bleeding	1 Days	Drug Withdrawn	Recovering

17	NL-LRB-240069, female, 10-20 Years, Consumer or other non health professional	Canesten Gyno 3 Vaginal creme 20Mg/G + 3 Applic 1 DF / 1 Days	Vaginal mycosis		Vaginal bleeding	2 Days	Not Applicable	Not Recovered
20	NL-LRB-00258653, female, 20-30 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 1 dosage form / 1 Days	Vaginal mycosis	Non specified spiraaltje	Vaginal haemorrhage	2 Days	Drug Withdrawn	Not Recovered
22	NL-BAYER-2018-148278, female, 10-20 Years, Consumer or other non health professional	Canesten Gyno 1 100Mg/G Vaginal cr In Applicat 5G	Vaginosis fungal NOS		Vaginal hemorrhage	-		Not Recovered
24	NL-BAYER-2019-079728, female, , Consumer or other non health professional	Canesten Gyno 1 100Mg/G Vaginal cr In Applicat 5G			Vaginal bleeding	2 Days		Unknown
25	NL-LRB-00347695, female, 20-30 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme ? mg/g 1 dosage form / Total	Vulvovaginal mycotic infection		Vaginal haemorrhage, Vaginal discharge	12 Hours 12 Hours	Drug Withdrawn	Not Recovered, Not Recovered
26	NL-LRB-00357020, female, 30-40 years, Consumer or other non health professional	Canesten Gyno Vaginal creme ? mg/g 1 gram / 12 Hours	Fungal infection after antibiotics		Bloody vaginal discharge, Abdominal cramp	6 Hours 6 Hours	Dose Reduced	Not Recovered, Not Recovered
33	NL-BAYER-2019-127435, female, , Consumer or other non health professional	Canesten Gyno Vaginalcreme 10% 100Mg/G			Vaginal discharge abnormality, Vaginal itching, Burning sensation			Unknown, Unknown, Unknown
36	NL-LRB-61424, female, 30-40 Years, Pharmacist	Canesten Gyno 3 Vaginal creme 20Mg/G + 3 Applic 2 DF / 1 Days		Fluconazole Capsule 150Mg	Intermenstrual bleeding	2 Days	Dose Not Changed	Recovered
37	NL-LRB-78124, female, 40-50 Years, Consumer or other non health professional	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 10 mg/ 1 Days	Vaginal candidiasis		Intermenstrual bleeding	2 Days	Dose Not Changed	Recovered with sequelae
38	NL-LRB-236372, female, 30-40 Years, Consumer or	Canesten Gyno Vaginal creme 10Mg/G + 6 Applicators 2 DF / 1 Days	Vaginal mycosis		Vaginal discharge	2 Days	Unknown	Not Recovered

	other non health professional							
2	NL-LRB-76908, female, 10-20 Years, Physician	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator 500 milligram /	Vaginal candidiasis		Vaginal bleeding	4 Days	Not Applicable	Unknown
7	NL-LRB-180941, female, 20-30 Years, Physician	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator 1 DF / 1 Days	Candidiasis		Vaginal haemorrhage	2 Days	Drug Withdrawn	Recovered
9	NL-LRB-194604, female, 10-20 Years, Consumer or other non health professional	Canesten Gyno 3 Vaginal tablet 200Mg + Applicator 200 mg / 1 Days	Vaginal mycosis	Non Specified O.A.C.	Vaginal bleeding	2 Days	Not Applicable	Recovered
11	NL-LRB-220534, female, 30-40 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator	Bleeding		Vaginal bleeding	3 Days	Drug Withdrawn	Not Recovered
12	NL-LRB-222988, female, 20-30 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator 1 DF / 1 Months	Vaginal mycosis	Non specified lichte pil	Vaginal haemorrhage	3 Days	Not Applicable	Unknown
13	NL-LRB-227433, female, 50-60 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator 1 dosage form /	Fungal infection	unspecifed	Vaginal haemorrhage	3 Days	Not Applicable	Recovered
21	NL-LRB-00289322, female, 50-60 Years, Consumer or other non health professional	Canesten Gyno 3 Vaginal tablet 200Mg + Applicator	Vaginal mycosis		Vaginal bleeding	2 Days	Not Applicable	Not Recovered
23	NL-BAYER-2019-081818, female, , Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator			Vaginal bleeding	-		Unknown
29	NL-LRB-243588, female 20-30 Years, Consumer or other non health professional	CANESTEN GYNO 3 VAGINAL TABLET 200MG + APPLICATOR 1 DF / 1 Days	Gardnerella infection		Fluor vaginalis	2 Days	Not Applicable	Recovered
30	NL-BAYER-2018-007449, female, ,	Canesten Gyno Vaginal tablet 500 mg	0,00		Vaginal discharge abnormality, Vaginal	6 Days 6 Days 2 Days		Unknown, Unknown

	Consumer or other non health professional				discharge abnormality	6 Days		
31	NL-BAYER-2018-090960, female, 10-20 years, Consumer or other non health professional	Canesten Gyno tablet	Vaginosis fungal NOS		Vaginal discharge	- -	Dose Not Changed	Unknown
32	NL-BAYER-2018-104882, female, 20-30 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator	Vaginosis fungal NOS		Vaginal discharge abnormality	2 Days 2 Days		Not Recovered
34	NL-BAYER-2019-137123, female, , Consumer or other non health professional	Canesten Gyno Vaginal tablet 1 dosage form / 1 Days	0,00		Vaginal discharge	2 Days		Unknown
39	NL-BAYER-2017-096795, female, , Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator	0,00		Genital bleeding, Vaginal discharge, Vaginal discharge abnormality, Offensive vaginal discharge	3 Days 2 Days 2 Days 3 Days		Unknown, Unknown, Unknown, Unknown
40	NL-BAYER-2019-038898, female, 30-40 years, Consumer or other non health professional	Canesten Gyno 1 Vaginal tablet 500Mg + Applicator Canesten Gyno Vaginalcreme 100Mg/G	Fungal infection		Genital bleeding, Vaginal discharge, Drug ineffective		,	Unknown, Unknown, Unknown
10	NL-LRB-212630, female, 10-20 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator 1 dosage form / 1 Total	Vaginal mycosis		Vaginal bleeding	1 Days	Not Applicable	Not Recovered
16	NL-LRB-238152, female, 50-60 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator 500 milligram / 1 Days	Vaginal mycosis	Non specified antibiotica	Vaginal bleeding	8 Hours	Not Applicable	Unknown
19	NL-LRB-231483, female, 40-50 Years, Consumer or other non health professional	Canesten Gyno 1 (capsule) 1 dosage form /	Vaginal candida	Cabergoline Tablet 0,5Mg	Vaginal haemorrhage, Lower abdominal pain	48 Hours 48 Hours	Not Applicable	Recovering, Recovering

27	NL-LRB-00360244, female, 20-30 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator 500 milligram / Total	Vaginal mycosis		Vaginal haemorrhage Abdominal pain lower, Low back pain, Nausea, Vomiting, Diarrhoea, Fatigue, Fever	1 Days 1 Days 1 Days 1 Days 1 Days 1 Days	Not Applicable	Not Recovered, Not Recov, Not Recov, No Recov, No Recov, No Recov
28	NL-LRB-00365736, female, 30-40 Years, Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator 500 milligram / 1 Days	Candida vaginal	Non specified OAC	Vaginal bleeding	1 Days	Not Applicable	Recovered
35	NL-BAYER-2019-143821, female, , Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator			Vaginal discharge abnormality	-		Unknown
41	NL-BAYER-2019-065297, female, , Consumer or other non health professional	Canesten Gyno 1 Vaginal capsule 500Mg + Applicator		Non Specified contraceptive	Heavy periods	-		Unknown
42	NL-BAYER-2018-134876, female, 40-50 Years, Consumer or other non health professional	Canesten vaginal capsule	Fungal infection		Vaginal bleeding	- -		Unknown
18	NL-LRB-247557, female, 40-50 Years, Consumer or other non health professional	Canesten Gyno Vaginaal ? mg/g 1 dosage form /	Candida infection		Vaginal bleeding, Uterine disorder	1 Days 1 Days	Not Applicable	Not Recovered, Not Recovered