



MULTI-GYN SUMMARY OF STUDIES

Contact details

BioClin BV

Eveline van Dijk

e.vandijk@bioclin.com

+ 31 (0)15 2512 895

JUNE 2014
BIOCLIN BV

CONFIDENTIAL

First line treatment and relief of Bacterial Vaginosis

– related vaginal complaints with Metronidazole and Multi-Gyn ActiGel

Published study in *European Obstetrics & Gynaecology*, Volume 7, Issue 2, Autumn 2012

Introduction

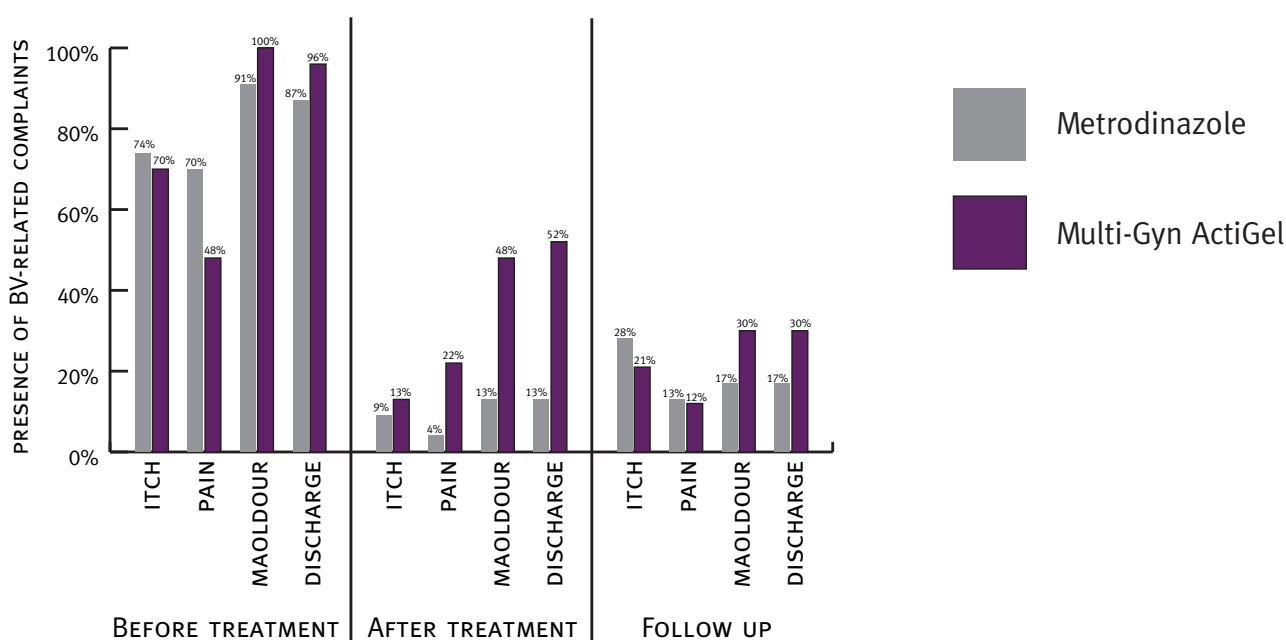
In an open label study conducted by Dr. Tatjana Bojovic, Dr. Djordje Bojovic, Dr. François-Xavier Boyer de La Tour and Dr. Babette Lamers, 47 age-matched women with Bacterial Vaginosis (BV) and related complaints received as first line treatment either a course of prescribed oral metronidazole or Multi-Gyn ActiGel intra-vaginally. Metronidazole is the standard treatment for BV, but this antibiotic has several drawbacks, including recurrency of infection, negative side-effects and risk for bacterial resistance. Therefore, the efficacy of Multi-Gyn ActiGel as a safe and natural alternative was assessed in comparison to metronidazole. Relief of BV-related complaints (itch, pain, malodour, excessive vaginal discharge) was assessed after 1 and 12 weeks.

Results:

Before treatment, about 70% of women with BV-related complaints reported itch and pain, and almost all women suffered from malodour and excessive discharge. After 1 week of treatment, both in the metronidazole as well as in ActiGel-treated group nearly all patients were completely relieved from itch and pain. Scores of malodour and discharge had also improved in almost all patients in both study groups after 1 week. These complaints were complete gone in about 85% and 50% of the metronidazole and ActiGel-treated patients, respectively.

At follow-up after 12 weeks, the number of ActiGel-treated patients completely relieved of malodour and excessive discharge had increased to about 70%. No side effects were reported in this study. Oral metronidazole was slightly more effective at one week post treatment; ActiGel was equally as effective as metronidazole at three months post treatment.

COMPLAINTS AS ESTABLISHED BY THE CLINICIAN



Conclusion

Both metronidazole and ActiGel were highly effective to treat BV-related symptoms. After 1 week treatment metronidazole was slightly more effective than ActiGel, but after 12 weeks both methods were equally effective. This study demonstrates that ActiGel could be an effective and safe alternative to metronidazole for treatment of BV-related complaints.

Multi-Gyn ActiGel Survey Italy

Observational Gynecologist and Consumer survey on the efficacy of Actigel in the treatment of uncomplicated vaginal conditions, 2012.

Introduction

The survey was conducted in Italy, by our partner Corman, in autumn 2012 with the collaboration of 102 gynaecologists and 98 pharmacies, which collected the treatment cards of 390 patients aged between 15 and 65. The gynaecologists worked with a VVS (Visual View Scale). The feedback of the patients was filled out in a VAS (Visual Analysing Scale) and sent back to the pharmacists. The survey design envisaged a 5-day treatment, morning and evening, with Multi-Gyn ActiGel and a daily compilation of the VAS to be returned to the pharmacist.

Results:

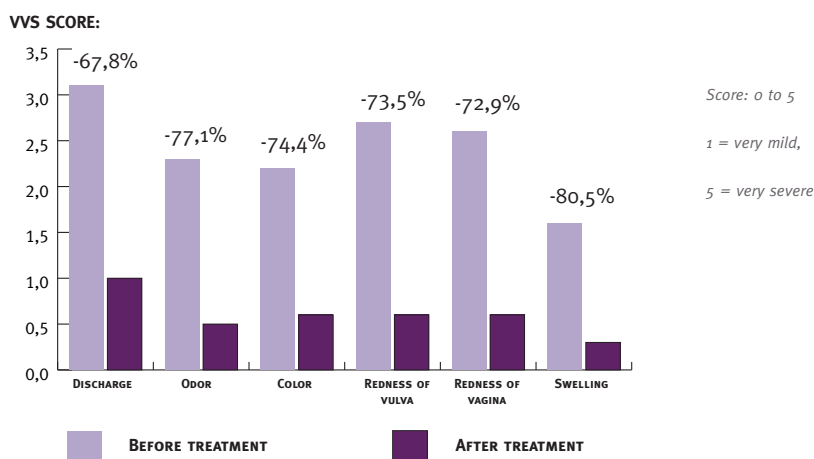
The scores were very similar for each age group and as a result we have grouped the results in two graphs. One graph with results of the gynaecologists and one graph with the results of the patients. The split of the results per age groups (and the corresponding graphs) can be found in the full survey report.

The results show a strong decrease of the initial complaints. Multi-Gyn ActiGel allowed the complete remission or the net improvement of the pathology.

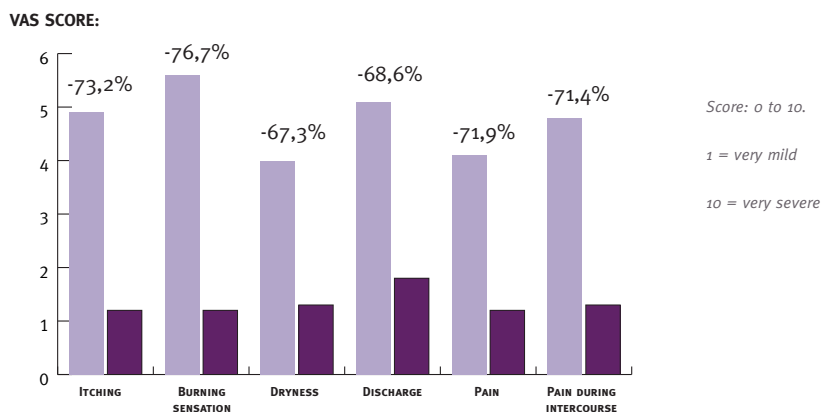
Conclusion:

RAPIDITY - ActiGel acts fast on itching, irritation and pain.

GYNECOLOGISTS EVALUATIONS OF SYMPTOMS AFTER 5 DAYS TREATMENT



PATIENTS EVALUATIONS OF SYMPTOMS AFTER 5 DAYS TREATMENT



EFFICACY - ActiGel has proven significant clinical efficacy in treating and preventing bacterial vaginosis at any age.

PREGNANCY AND LACTATION - ActiGel is safe to use during pregnancy and lactation. ActiGel does not contain perfumes or animal-based ingredients; it does not contain aggressive chemical substances, preservatives or hormones and is safe and harmless.

INTERACTION WITH MEDICATION & ALCOHOL - ActiGel does not interact with medication and alcohol.

TOLERABILITY PROFILE - ActiGel has no side effects and no adverse events have been recorded even in the event of accidental ingestion.

Multi-Gyn ActiGel Japanese study

Report on an exploratory study with ActiGel for women with vaginal discomforts. Tokyo, Japan 2013

Introduction

In a study conducted by Kunio Kitamura, MD et al. (2013), the efficacy and safety of Multi-Gyn ActiGel was evaluated. This study was conducted in 5 clinics in Tokyo with women complaining of vaginal discomforts. Ten samples of ActiGel were distributed to each of the 5 clinics aiming for 10 study cases per clinic.

Before they were enrolled in the study, each patient was asked about the history of their vaginal discomforts, the frequency of occurrence and treatment history. During the first visit the expected efficacy and possible adverse effects of ActiGel were fully explained to the patients. The study was conducted over a period of 3 months (October '12 to January '13).

Results:

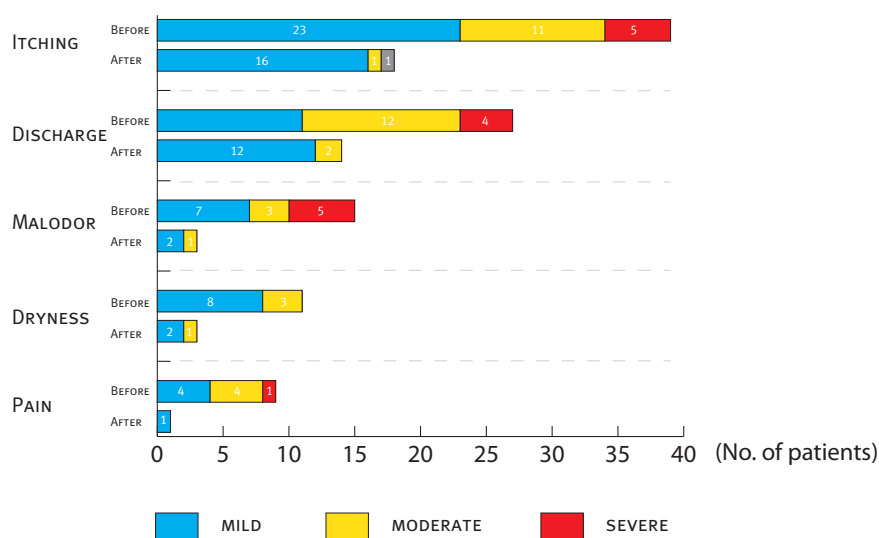
As a result of this study it was found that ActiGel is effective in women suffering from vaginal discomforts.

ActiGel improved the main symptoms that many of the women suffered from:

- Itching 43%
- Vaginal discharge 60%
- Malodor 7%

It is important to mention that no adverse effects were observed in any of the women.

SYMPTOM-BY-SYMPATOM CHANGE IN THE NUMBER OF PATIENTS WITH VAGINAL DISCOMFORTS



Conclusion:

From these findings, ActiGel is considered effective in women suffering from vaginal discomforts. In particular, satisfactory effects were observed on “itching”, “vaginal discharge” and “malodor” being the symptoms that many women suffer from. This efficacy on Bacterial Vaginosis-related complaints was also supported by the vaginal pH data obtained from 9 patients. The mean vaginal pH values in 9 patients decreased from 6.2 to 4.7. In consideration of this pH change

and the above mentioned changes in the symptoms, the improvement of vaginal discomforts was considered to have been presented by re-balancing of vaginal flora and recovery of vaginal self-purification effects.

ActiGel was useful for women with vaginal discomforts, and it was also useful as a supportive cure to the drugs for the underlying diseases such as Bacterial Vaginosis (non-specific vaginitis) and Candida vaginitis.

A pilot study to evaluate the efficacy of Multi-Gyn ActiGel in the treatment of nonspecific vulvitis and vaginitis.

Unpublished controlled clinical trial by BioClin B.V, Delft, May 1996.

Dr. G. Beyer, Dr. W. F. Beelaarts van Blokland, Dr. R. M. Gaaymans, Dr. M. C. Dersjant, Dr. M. Csanky, Dr. M. E. Boon and Dr. D. Goedhart. Unpublished controlled clinical trial by BioClin B.V, Delft, August 2006.

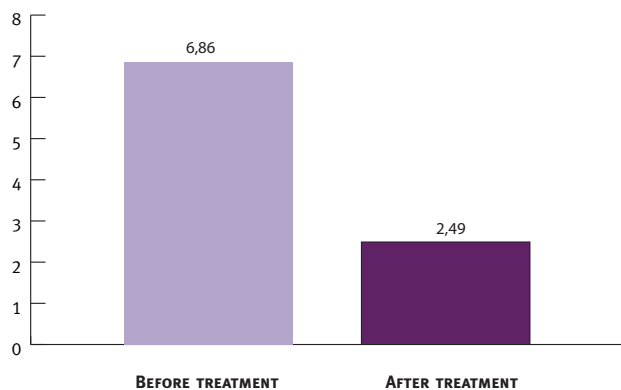
Introduction

The objective was to investigate the efficacy of the application of Multi-Gyn ActiGel for the relief of the symptoms of nonspecific vulvitis and vaginitis.

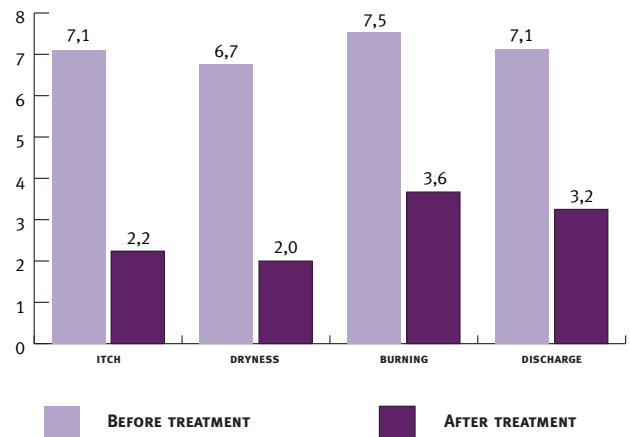
In a pilot study, conducted by Dr. G. Beyer, et al. (2006) the efficacy of Multi-Gyn ActiGel in the treatment of nonspecific vulvitis and vaginitis was evaluated via VAS scores of 50 patients.

The complaints were evaluated by the Visual Vagina/Vulva Score as made up from the sum of the number given by the investigator for discharge, smell of the discharge, color of the discharge, redness of the vagina and vulva and the swelling of this area, the VAS score in which the patient indicates the seriousness of the complaints with a point on a scale of 0-10 and the Trouble score in which the patient expresses the seriousness of the complaint in a cipher. The patient was asked to apply the product during one week and to return in 2 weeks for a control visit. The patient was to report daily in the patient diary on the seriousness of the complaint with the use of the VAS Score and the Trouble Score number and to comment on the treatment.

MEAN VAS-SCORE OF ALL COMPLAINTS BEFORE AND AFTER TREAT



MEAN VAS VALUES PER COMPLAINT



0 - 10, 0 = no complaint, 10 = most severe complaints

Results:

64 % of participants reported positive results after one week of treatment. Disappearance of vaginal complaints in 16 participants

Side effects; none

An In Vitro Study of the Effects of 4 Self Care Gels on Desirable and Undesirable Vaginal Microbiota

Joke AM Dols and Mathilde E Boon, *European Obstetrics & Gynaecology*, 2012;7(2):107–10

Introduction

Vaginal self care gels are used to relieve and treat vaginal discomforts and to maintain and restore the healthy vaginal flora and pH. The effects of four vaginal self care gels (RepHresh, Gynofit, Balance Active, Multi-Gyn ActiGel) on desirable and undesirable vaginal microbiota were evaluated in a challenge study.

Vaginal self care gels are used to relief and treat vaginal discomforts. All intend to restore and maintain the optimal pH and the vaginal flora. Such products should therefore not have a negative impact on the lactobacilli. After achieving the desired pH the lactobacilli should take over and continue to maintain the pH with their production of lactic acid. Also, the product should not allow the overgrowth of *Candida albicans*.

In case a product eliminates all flora, the BV-associated as well as the lactobacilli, it is to be considered a vaginal disinfectant, a microbicide. We present the in vitro test results of a kinetic challenge test model.

Four OTC vaginal gels which are widely available for intimate self care were tested. We focus on the suitability and safety of these vaginal gels by investigating their impact on six lactobacillus strains, four strains of BV-associated bacteria, and *Candida albicans*. In vitro testing of self care vaginal gels is a useful tool to predict their effects in vivo and we propose that this testing would be advisable

All vaginal gels tested had the desired impact on the coccoid bacteria. However, RepHresh, Balance Activ, and Gynofit all appear to be highly bactericidal against both homo- and heterofermentative lactobacilli

in vitro. This could be seen as an adverse event of the use of vaginal gels, and should be considered in the decision of using such gels.

Multi-Gyn ActiGel showed to have the smallest negative impact on the lactobacilli flora. The challenge test results show that Balance Activ, Gynofit, and RepHresh cannot be expected to sustain the optimal vaginal pH

because lactobacilli are quickly decreased. It can be expected that these products will require continuous application to continuously install a low pH with the acidity of the product and that this task will not

be taken over by the lactic acid production of lactobacilli. With respect to *Candida*, Balance Activ, ActiGel, and Gynofit reduce *Candida*. The increase of *Candida* by the use of RepHresh was a remarkable adverse effect found.

Results:

Exposure to RepHresh, Gynofit and Balance Activ resulted in a decrease in lactobacilli. Multi-Gyn ActiGel does not substantially affect lactobacilli.

Candida was decreased by exposure to Gynofit, Balance Activ and Multi-Gyn ActiGel. Exposure to RepHresh resulted in an increase.

Conclusions:

Based on the data of this in vitro study, it appears to be unlikely that Balance Activ, Gynofit, and RepHresh will have the desired effect of restoration and maintenance of healthy vaginal microbiota. Multi-Gyn ActiGel shows the least noxious effect on the lactobacilli and therefore seems to be the most suitable product. RepHresh stimulates the growth of *Candida* and therefore it seems to be the least suitable product.

Short report of the Multi-Gyn FloraPlus pilot study

A pilot study to evaluate the efficacy of Multi-Gyn FloraPlus for the control of the exacerbation of Candida, September 2012

Introduction

This evidence based pilot study evaluated the in vivo effects of the application of this prebiotic vaginal gel.

1. Primary objectives: to assess the efficacy of FloraPlus for the prevention of the exacerbation of the presence of *Candida albicans* in the vaginal flora.
2. Secondary objective: to assess the safety of the 5 days application of Multi-Gyn FloraPlus.
3. Tertiary objective: to assess the effect of Multi-Gyn FloraPlus on the *Candida*-related vaginal complaints.

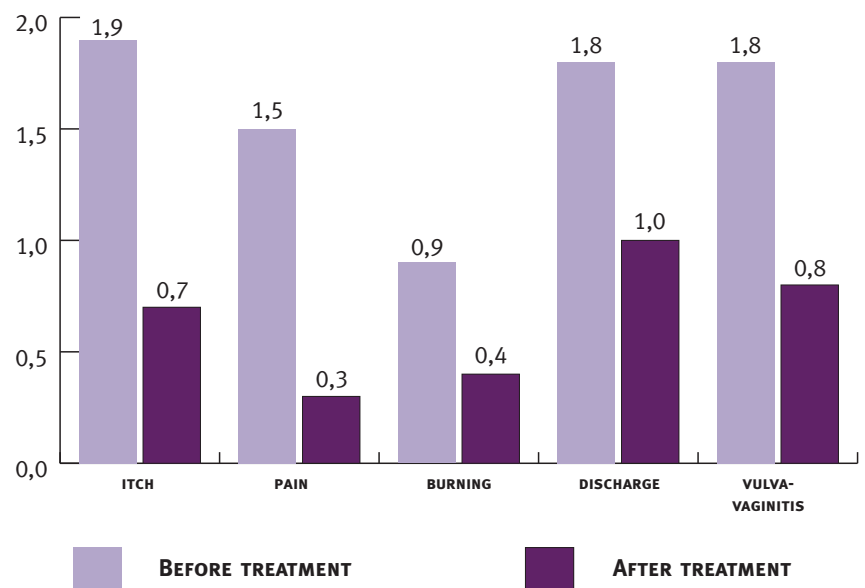
Method:

The Gynecological practice of Dr. Bojovic, Belgrade, Serbia was used for this study and 26 female patients were evaluated (women to whom the investigator would routinely prescribe a topical anti-mycotic cream).

The study results were evaluated with the following parameters:

1. Vulvovaginitis as diagnosed by the investigator
2. *Candida* as diagnosed by the LCPL laboratory (located in Leiden, The Netherlands)
3. Abnormal discharge
4. Itch as perceived by the patient
5. Pain as perceived by the patient

MEAN VALUES OF ALL COMPLAINTS



Score 0 to 3, mild=1, moderate=2, severe=3

6. Burning as perceived by the patient
7. Treatment results as judged by the investigator
8. Treatment satisfaction as judged by the patient for the relief of symptoms

Additionally the patients were asked for their opinion of Multi-Gyn FloraPlus with respect to the consistency and application of the product.

Conclusion:

It is clearly shown that the approach of competitive growth with the stimulation of the beneficial commensal flora of lactobacilli is efficacious in a great number of patients with diagnosed candidiasis.

The relief of candidiasis-related complaints was very good.

Multi-Gyn FemiWash

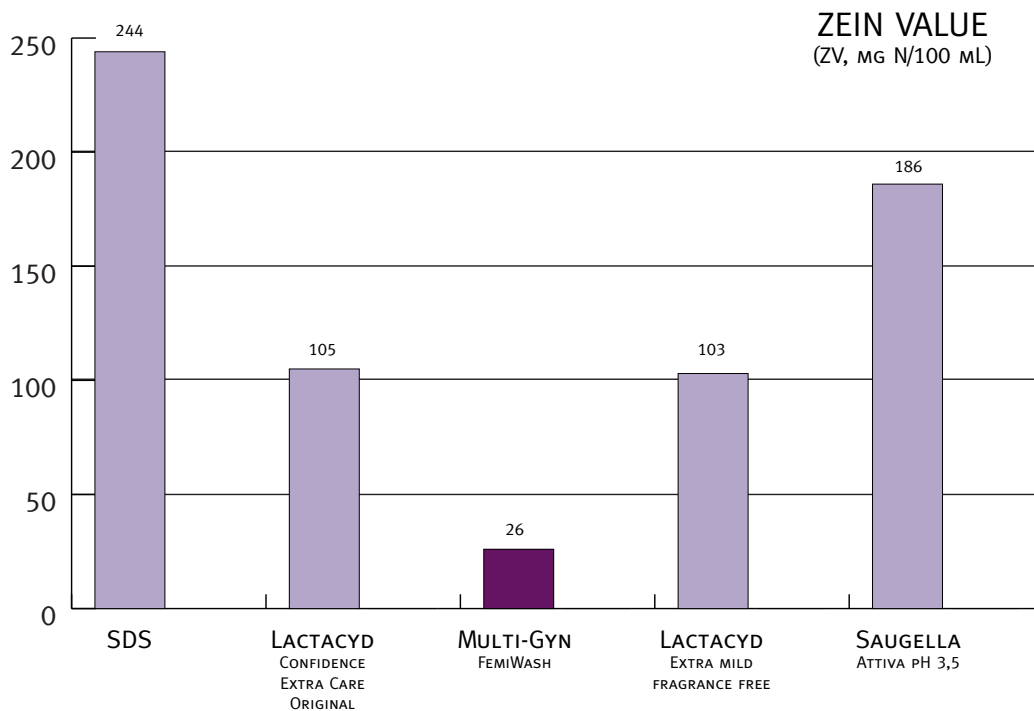
Skin irritation test for Multi-Gyn FemiWash, performed by Kao Chemicals Europe (Barcelona, Spain), 2005

Introduction

BioClin evaluated the eye and skin irritation of 4 intimate wash product samples.

To evaluate the potential of skin irritation we have followed the Zein test and to evaluate the potential of eye irritation potential we have followed the Red Blood Count test (RBC).

In order to gain an understanding of the effects, such as skin irritation and protein denaturation, of surfactants that are common in personal care products the Zein test was concluded. In this test the Interactions of a model surfactant, sodium dodecyl sulfate (SDS), with a water-insoluble model protein, zein, were investigated and has given the scores that are shown in the graph. For more information on this test, please contact Diana Pasho.



Results:

Multi-Gyn FemiWash is by far the best intimate wash on the market. According to the zein values, Multi-Gyn FemiWash is 7 times better than the other tested intimate wash samples.

Swiss survey Multi-Gyn IntiFresh

Our Swiss partner Hygis conducted a survey amongst women of all ages who were eager to try the new Multi-Gyn IntiFresh intimate wipes. Hygis also questioned women about Multi-Gyn IntiSkin spray. The results were very positive.

Some of the key results from the 98 women who sent back the survey on **Multi-Gyn IntiFresh**:

- The women preferred Multi-Gyn IntiFresh to competing intimate wipes brands.
- They indicated that the discomforts they had before using Multi-Gyn IntiFresh, diminished significantly after using the intimate wipes. Multi-Gyn IntiFresh scores very high on satisfaction when it comes to scent, quality and sensation of freshness.
- All women said that they would definitely recommend Multi-Gyn IntiFresh to their friends. Furthermore, they would like to continue using the wipes in the future.

Multi-Gyn IntiFresh scores a **8,5** out of 10 for the odour of the wipe

and a **8,9** out of 10 on sensation of freshness

"Long lasting feeling of freshness, especially after working out"

92% would use Multi-Gyn IntiFresh again and 94% would also recommend it!

Swiss survey Multi-Gyn IntiSkin users are more than satisfied

Some of the key results from 10 women who sent back the survey on **Multi-Gyn IntiSkin**:

- The women all indicated that their discomforts, such as itching and irritation, diminished after using Multi-Gyn IntiSkin.
- 8 women indicated that they would like to continue using Multi-Gyn IntiSkin after the test.
- 8 out of 10 women gave the score 8 or higher.



"Excellent product. I don't have any problems with rash after shaving anymore and my vaginal malodour diminished considerably. I couldn't be more satisfied with this product"