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USEFULNESS OF NEO SAMPOON

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USEFULNESS OF NEO SAMPOON

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USEFULNESS OF NEO SAMPOON

1.0 Summary

Neo Sampoon is a spermicidal foaming tablet contraceptive developed by Eisai Ltd. of Japan in the 1960's. The usefulness of any method of contraception is judged by its safety, acceptability and effectiveness. Available data suggest that Neo Sampoon is a safe and effective method of contraception. Its acceptability, however, seems highly variable, as evidenced by the large country to country variation in continuation rate and users' failure rate.

Neo Sampoon has a special clientele in community based (free or subsidized) distribution programs. It has the potential of serving a sizable portion of lactating mothers, of women with infrequent coitus, and of women who reject oral contraceptives and condoms. The projected importance of Neo Sampoon is seen from the fact that in developing countries the first of these three groups alone can represent about one fifth of all married women of reproductive ages. Little data exists on the characteristics of Neo Samppon or other spermicide purchasers. In West Germany, which probably has the highest spermicide usage rate in the world, spermicides are especially popular with young unmarried women.

2.0 Use

Like other spermicidal foaming tablets, Neo Sampoon must be inserted deep into the vagina approximately five minutes prior to intercourse. The tablets generate foam as soon as they come in contract with vaginal fluid. The foam distributes itself throughout the vagina and acts as a chemical and mechanical barrier to immobilize sperms and prevents their passage through the cervix, thus preventing fertilization (see Appendix 1 for instructions on its use).

3.0 Safety

The spermicidal ingredient in Neo Sampoon tablets is Menfegol (TS-88) which is a non-ionic surfactant developed by Eisai Ltd. Of Japan. Since 1969 Menfegol has been marketed at a dose level of 60 mg in Neo Sampoon tablets. Assuming an average weight women as 50 - 60 Kg, the maximum exposure per use would be approximately 1 mg/Kg. Drug safety studies were conducted by Eisai which evaluated the toxicity in lab animals. These drug safety studies support the safety of Menfegol as a vaginal contraceptive, and also in the case of accidental oral ingestion. A summary of Eisai's experimental results is present in Appendix 2.

4.0 Acceptability

Acceptability of a contraceptive method is commonly measured as a continuation rate over a unit interval of time.

4.1 Continuation Rate

Continuation rate data for Neo Sampoon are scanty. The few available clinical studies indicate highly variable continuation rates as examplified by the Japanese and the Colombian experiences (Table 1).

Women in these clinical studies were similar in age (mostly 20-35) and parity (2-3 living children); however, they were vastly different in social economic status, rural/urban residence and prior contraceptive experience. The reasons cited for dropping out these studies were relocation of family, desire for another child, anxiety over the effectiveness of Neo Sampoon, and presence of side-effects.

The continuation rate is probably very much a function of the staff providing the contraceptive as it is a function of the women accepting it. The importance of family planning personnel is evident from milti-center clinical trials which find that complaints about side effects vary greatly from one center to another. In a study in Manila, one clinic experienced only about half as many complaints and one-fifth as many discontinuations for side effects as two other clinics (9). In Guatemala, Galich observed that when medical and paramedical personnel are familiar with Neo Sampoon, demand for the product increases (11). When health personnel inform acceptors in advance, for example, that spermicides will provide additional lubrication and that foaming tablets may generate a feeling of warmth, the effects can be depicted as benefits rather than disadvantages (4).

4.2 Side Effects

The frequency of side-effects reported in various studies is presented in Table 2. It is consistently shown that no serious side-effects were reported in any of the clinical studies. The most common side effects were an increase of vaginal discharge, and a subjective sensation of warmth in the vagina, which signals the start of dissolution of the tablet. The warm feeling was considered by some women to be uncomforable, but by other women to be pleasurable.

A large portion of Japanese women reported many side effects including heat, but most of them also claimed that these were not troublesome. In contrast a small portion (20%) of the Colombian women reported side effects, but 44% of all users discontinued after only one month (15).

Thus the negative perception of a side effect may be a more relevant factor than the frequency of the side effect in determining continuation of use. Some understanding of the cultural perception on those frequently reported side effect would be desirable prior to mass marketing or distribution of Neo Sampoon.

5.0 Failure Rate

The failure rate measures the number of pregnancies per 100 women - years of exposure (WYE) to a contracetive method. One measure of failure rate is the Pearl Index:

$$\text{Pearl Index} = \frac{\text{number of pregnancies}}{\text{women months of use}} \times 1200$$

The major short-coming of the Pearl Index is that it is sensitive to the duration of observation. The Pearl Index for a group of users is likely to improve over time simply because the unsatisfied users or irregular users have dropped out of the study due to pregnancy or switching to other methods.

A better measure of failure rate, one which controls for the duration of use, is a life table rate. Basically, a life table can be viewed as a column of numbers which specify the percentage of women who are still using a contraceptive after 3,6,9, 12 ... months since initiation of use. "Clearly, there are many ways to exit from a contraceptive life table: one may become pregnant, or stop use for medical or personal reasons. For the purpose of isolating events of interest, an associated single decrement life table may be computed from the information contained in the multiple decrement life table. Resulting pregnancy rates when all other causes of discontinuation have been eliminated are called gross rates, while those obtained for the multiple decrement table are called net rates " (3).

Unfortunately, life table pregnancy rates for Neo Sampoon are, for the most part, unavailable.

5.1 Pearl Index from Clinical Studies

The pregnancy rates (Pearl Index) from ten clinical studies involving four countries are presented in table 3 and summarized below:

Japan:	2.3, 2.8, 3.2, 4.4, 6.8
The Philippines:	6.7, 7.8, 7.9
Bangladesh:	8.7
Sweden:	20.2

The three Asian countries display respectably low failure rates ranging from 2.3 - 8.7. Which compare favorably with the other contraceptive methods used by U.S. women (see table 4). The Swedish rate of 20.2 is relatively high, especially if Neo Sampoon is replacing potential pill and IUD users; however, consider the chance of pregnancy of a sexually active non-contracepting woman being around 90 per 100 WYE, pregnancy rate of 20 still offers considerable, though not great, protection.

Although the failure rates from the three Asian countries look quite good, they should be interpreted with caution. The subjects in some of these studies were selected for high motivation, prior experience in spermicidal contraceptives (10, 12, 17, 19, 20), or good education (9, 18). Thus these pregnancy rates should be viewed as expressing the maximum effectiveness of Neo Sampoon.

Data suggest that Neo Sampoon is culturally selective in terms of its acceptance, continued use and regularity of use. It is not clear which are the traits conducive to successful use, although one notices that of those successful Japanese users many are former condom or foaming tablet users, thus experienced with the coital related methods like Neo Sampoon. (See Table 5).

5.2 Method vs. User Failure

Failure rate can be attributed to either the contraceptive or to the users, although the demarcation is often murky. Method failure refers to accidental pregnant cases which occurred during regular contraceptive practice. That is, vaginal contraceptives were used in each and every act of intercourse. Method failure includes pregnancies which occur with incorrect use. User failure includes pregnancies in which vaginal contraceptives were not used at every intercourse.

Available data show that in Neo Sampoon the user failure rate is always greater than the method failure rate, and that there are pronounced cross-cultured differences on the users' failure rate, but less so on the method failure rate.

A recent review article on all spermicidal contraceptives affirms the above observation (4). An overall failure rate of 15 per 100 women - years of exposure is estimated, and the user failure rate is at least twice that of the method failure rate.

5.3 Loop vs. Disc Tablets

The Swedish (actually Sweden and Holland) study exhibits an unusually high rate of method and user failure compared with the Asian studies. Although Eisai claims there is no difference in efficacy, one possible explanation is that the Neo Sampoon disc tablet which was used in the Swedish study does not work as well as the loop tablets used elsewhere.

Eisai insists that for individual packaging it is necessary to switch from the loop type of tablets to the disc type; that this is necessary to minimize breakage. Broken tablets would be difficult to insert, and the disc type could withstand four times as much pressure as the loop type. Eisai also stated that the disc will not require more time to dissolve, and both types of tablets produce equal amount of foam. The primary differences between the disc and the loop tablet are:

a. The disc contains foam stabilizer; the loop does not.
b. The loop has a higher surface to volume ratio than the disc.

Other differences are shown in Appendix 3. Further clinical studies are needed in order to determine whether there indeed is a difference between Neo Sampoon loop and disc tablets. These studies can be conducted in places where control population already exists. For example giving another group of Swedish women loop tablets, or giving the Dacca women disc tablets.

5.4 Failure Rate of Condom as a Comparison

Table 6 presents condom failure rate (Pearl Index) from 24 studies conducted in the US, Britain, India, Puerto Rico and Korea. It displays an even wider spread in failure rate (3 to 36 per 100 years of exposure) than Neo Sampoon. The reasons for this include:

a. different kinds of condoms used contributing to differences in method failure rate.
b. cross cultural differences in the success of condom users (contributing to the users' failure rate).
c. differences in data sources (clinical study vs. survey).
d. varying proportions of condom users using adjunct methods.

The majority (about 70%) of the condom users also utilize other contraceptive methods. Therefore the reported failure rate is not for condom alone, but condom plus some other method such as rhythm or foam tablets.

This points to the problem of using a survey to determine the effectiveness of a coital method such as condom or Neo Sampoon. One may be looking more at the effect of rhythm than of Neo Sampoon (or condom). A more precise way to define the use effectiveness of Neo Sampoon is through controlled clinical studies.

6.0 Client Characteristics

Women at different stages of reproductive life may choose to use different contraceptive methods. For example, sterilization is used after achieving the desired family size. Spermicides are usually used for spacing births. In the community based distribution project Neo Sampoon is given mainly to lactating women, women with infrequent coitus, or women who refused oral contraceptives and condoms. It is hypothesized that women probably use it over a limited period of time; that it is probably used not as a sole method but as an adjunct method with rhythm or other barrier methods. Thus Neo Sampoon is probably not used with great regularity.

There is little information about the people who buy Neo Sampoon through commercial retail sales. It is speculated that because spermicides are used only at intercourse and are easily available through commerial channels, they are particularly convenient for young women who have intercourse infrequently (4, P. 83). Reportedly these reasons help explain why spermicides are especially popular with young, unmarried women in countries where spermicides are vigorously promoted, such as West Germany.

7.0 Discussion

In any population, one finds a varying portion of women who prefer an occasional method of contraception, a local method, or who find spermicides a useful back-up to another method. To them, Neo Sampoon offers a viable alternative. Neo Sampoon used regularly is a safe and effective method of birth control. In countries where abortion is legal or safe abortion is accessible, the combination of vaginal barrier methods with first timester abortion presents less risk to the user than adopting IUDs or oral contraceptives. (21).

Data suggest that the acceptors do become accustomed to the side effects as time goes on, and the frequency of complaints declines (13, 14). The warm sensation and sometimes, a ticklish feeling, did not seem to deter sexual pleasure; however, the dissolution time appeared to raise a problem which is shared by other vaginal contraceptive tablets. An ample contraceptive effect cannot be attained unless dissolution immediately precedes ejaculation. The timing can be a mental burden to some people, and this appears to have been the reason why tablets have been rejected by some.

The data collated in this report are meant to give a general idea on the usefulness of Neo Sampoon. Comparisons among studies should be viewed with caution because methods of computation used in these studies are not necessarily the same. For example:

a. In computing continuation rate, different assumptions may have been made on women who failed to return for follow-up.

b. In some studies discontinuation rate is computed by the life table method; in other studies, it is simply reported as a ratio of drop-outs to the total number of participants over a period of time.

c. Studies which evaluate side effects early on will tend to get more complaints than those evaluating at the end of the study. This is because the frequency of side effects reported seemed to decline overtime, possibly due to drop out of the dissatisfied users, women got used to it, or she did not bother mentioning the same side effect at the later interview if she had already complained of the same previously.

d. Women who were recruited for a clinical study but did not use the method at all maybe considered as drop-outs in one study; in another study they might be removed from the denominator all together thus not considered as drop-outs.

TABLE 1

CONTINUATION RATE OF NEO SAMPOON USERS IN VARIOUS STUDIES

LOCATION OF STUDY	REF. NO.	CONTINUATION RATE (%)	TIME INTERVAL
Dacca, Bangladesh	14	70*	1 year
Swenden & Holland	13	73	1 year
Colombia	15	56	1 month
Philippines	9,18	76*	1 year
Japan	19	88	1 year
Japan	12	79	1 year
Japan	10	49	1 year
Japan	20	64	1 year
Japan	17	49	13 months

*Life Table rate

TABLE 2

SIDE EFFECTS REPORTED BY NEO SAMPOON USERS AND PERCENT OF WOMEN REPORTING EACH SIDE EFFECT IN NINE STUDIES

	LOCATION OF STUDY (REF. NO)								
	JAPAN	JAPAN	JAPAN	JAPAN	JAPAN	PHILIPPINES	BANGLADESH*	COLOMBIA*	SWEDEN/HOLLAND*
SIDE-EFFECTS	(10)	(20)	(8)	(17)	(19)	(9,18)	(14)	(15)	(13)
Warmth/heat/burning	42	50	53	43	100	61	26	17	12
Increase of discharge/ Leukorrhea	21	32	24	30	29			2	
Headache						16			
Vomiting/Anorexia						8			
Itch	2		2	2					
Irregular menses									
Coarse feeling		11		6				2	
Poor sexual feeling	7	4	4	4	3				
Inconvenience	2		4	3	2				
Improved Sexual feeling	33								
Other						4	6		

*EVALUATED AFTER ONE MONTH OF USE

TABLE 3

FAILURE RATES (PREGNANCIES PER 100 WOMEN YEARS OF USE) OF NEO SAMPOON FOAMING TABLETS IN SELECTED STUDIES

Author & Date	Ref No.	Location of Study	Characteristics of Population Studied	No. of Women	Woman-months of use	Average Duration of use (mos.)	No of Pregnancies	Failure Rates	
								Method Failure	Method & User Failure
Furusawa et al. 1968	10	Japan	Clinic pop. age 25-35	124	1,038	8.5	2	0	2.3
Ishihama & Inoue 1972	12	Japan	Farmer's wives	587	8,955	15.3	24	0.67	3.22
Colepias, 1978	18	Manila Philippines	Clinic pop., mean age 32.5, mostly college ed., monthly follow-up (FU)	60	N/A	14	4		6.67
Flavior et al. 1979	9	Manila Philippines	Clinic pop.,mean age 31.5, educated, monthly FU	587	N/A		33	3.8	7.9
Ohtani & Kawagoe 1967	19	Japan	Clinic pop., age 20-39, 2-3 children	74	816		3		3.6
Nagano, 1967	17	Japan	National Railway Employees & Family	116	1,298	11.2	3		2.8
IFRP 1979 (on going)	6 14 16	Dacca Bangladesh	Clinic pop., FU at 1, 3, 6, 12 month	150	831		6		8.7
Ortho pharmaceutical, 1979 (on going)	13	Sweden & Holland	Clinic pop.	342	1,186		20	6-10	20.2
Okuyama et al. 1968	20	Japan	Former vaginal contraceptive users	56	546	9.8	3	0	6.8
Lopez et al. 1979 (on going)	15	Bogota Columbia	Clinic pop., women of low SES, half with no contracept. experience	169			3	N/A	N/A

TABLE 4

EFFECTIVENESS OF VARIOUS CONTRACEPTIVE METHODS:
THEORETICAL AND ACTUAL USE RATES
Number of Pregnancies During the First Year of Use
per 100 Non-Sterile Women Initiating Method

Method	Used Correctly and Consistently	Average U. S. Experience Among 100 Women Who Wanted No More Children
	THEORETICAL EFFECTIVENESS	ACTUAL USE EFFECTIVENESS
Oral Contraceptive (combined)	0.34	4[a]-10[b]
I.M. Long-Acting Progestin	0.25	5-10
Condom + Spermicidal Agent	Less than 1[c]	5
Low Dose Oral Progestin	1-1.5	5-10[b]
IUD	1-3	5[a]
Condom	3	10[a]
Diaphragm (with spermicide)	3	17[a]
Spermicidal Foam	3	22[a]
Coitus Interruptus	9	20-25
Rhythm (Calendar)	13	32[a]
Lactation for 12 months	25	40[d]
Chance (sexually active)	90[e]	90[e]
Douche	?	40[a]

[a] Ryder, Norman B., Contraceptive Failure in the United States, Family Planning Perspectives 5:133-142, 1973.

[b] Oral contraceptive failure rates may be far higher than this, if one considers women who become pregnant after discontinuing oral contraceptives, but prior to initiating another method.

[c] Data are normally presented as Pearl indices. For conversion to the form used here, the Pearl Index was divided by 1300 to give the average monthly failure rate n. The proportion of women who would fail within one year is then $1-(1-n)^{12}$.

[d] Most women supplement breast feedings, significantly decreasing the contraceptive effectiveness of lactation.

[e] This figure is higher in younger couples having intercourse frequently, lower in women over 35 having intercourse infrequently.

SOURCE: R. A. Hatcher et al. Contraceptive Technology 1978-197. 9th Revised Edition, P. 29.

TABLE 5

PREVIOUS CONTRACEPTIVE HISTORY REPORTED BY NEO SAMPOON USERS, PERCENT USING EACH METHOD

LOCATION OF STUDY (REFERENCE NO.) / METHOD USED	PHILIPPINES (9,18)	COLOMBIA (15)	BANGLADESH (14)	JAPAN (20)	JAPAN (19)	JAPAN (17)
Never used	13.3	47.6	48			3
OC	50	12.2	41.3			
IUD	18.3	32.7	3.3		5.2	
Foam Tablet	13.3	4.1		100.0	23.1	50
Condom	10	0.7	6.0	83.9	38.8	42
Rhythm	45	0.7*	0.7	40.3	7.5	
Withdrawal	13.3				3.7	
Diaphragm/ Cervical Cap			0.7			
Pessary Method				13.5	9.0	3
Jelly				17.3	9.7	2

*Include Rhythm and Withdrawal.

TABLE 6

Pregnancy Rates per 100 Years of Exposure Using Condoms by Selected Characteristics of Couples or Married Women, in Major Studies Published between 1939-1972

Year of Publication	Locality or Name of study	Characteristics of Married Population Studied	Number of Couples or Women in Study or in Each Segment of Study	Percent of Couples using Condoms Alone	Years of Exposure with Condoms	Pregnancy Rate per 100 years of Exposure with Condoms
1969	Great Britain	Study of clinic records of couples participating in a male oriented fertitily control project. Wives have had at least four pregnancies in last six years and one live birth in previous twelve months.	53	100	129	3
1972	Great Britain	In depth follow up survey of couples married for five years. Initial intentions on family size compared with actual experience.	287	33	308	4
1953	Indianapolis Study	Survey of high income urban couples married in 1927-1929 with husbands under 40 and wives under 30 at time of marriage.	329	29	586	6
1953	Indianapolis Study	Survey of medium income urban couples married in 1927-1929 with husband under 40 and wives under 30 at time of marriage.	569	31	1,213	6
1940	New York	Study of clinic records of moderate income couples married an average of 10 years and who were provided with contraceptives. Sample selected from only one borough of New York City	932	14	204	6
1944	North Carolina	Study of a representative sample of rural couples with contraceptive experience and in need of contraceptive counselling.	295		297	6

TABLE 6 (continued)

1953	Indianapolis Study	Survey of fecund urban couples married in 1927-1929 with husbands under 40 and wives under 30 at time of marriage.	1,444	29	2,703	7
1953	Indianapolis	Survey of low income urban couples married in 1927-1929 with husbands under 40 and wives under 30 at time of marriage.	543	26	905	8
1939	Cincinnati	Study of records of low income urban married women who attended clinics.	491	7	325	10
1944	North Carolina	Study of a representative sample of rural couples with or without contraceptive experience.	658	59	649	11
1961	Family Growth in Metropolitan America	Survey of couples sampled from eight large urban areas who recently experienced a second birth. Analysis of contraceptive experience before the second and third pregnancies.	1,165	29	3,227	12
1959	Calcutta	Survey of couples representative of Bengali-speaking upper class, married only once. Age of wives below 40 at time of survey.	238		419	12
1944	North Carolina	Study of a representative sample of rural couples without contraceptive experience and in need of contraceptive counseling.	363		307	16
1961	Family Growth in Metropolitan America	Survey of couples sampled from eight large urban areas who recently experienced a second birth. Analysis of contraceptive experience before first pregnancy.	1,165	35	3,227	17
1940	New York	Study of clinic records of moderate income couples married an average of 10 years and who had not been provided with contraceptives. Sample selected from only one borough of New York City.	991	31	1,619	19

TABLE 6 (continued)

1942	West Virginia	Analysis of project which provided contraceptive services to married women aged 15 to 44 of high parity, after enlisting in project.	1,319	9	102	19
1939	Cincinnati	Study of clinic records of low income urban married women prior to acceptance of clinic contraceptive services.	1,621	24	1,551	23
1959	Calcutta	Survey of couples representative of Bengali-speaking population married only once. Age of wives below 40 at time of study.				23
1966	Bombay	Analysis of clinic records of young, fertile, low income couples recruited into family planning clinics.	6,877	6	265	24
1959	Calcutta	Survey of couples representative of Bengali-speaking middle class, married only once. Age of wives below 40 at time of survey.	459		444	25
1961	Puerto Rico	Study of young, married women of low income, rural background who were provided with contraceptive services.	1,007	19	7,963	28
1959	Calcutta	Survey of couples representative of Bengali-speaking laboring class, married only once. Age of wives below 40 at time of survey.	321			
1942	West Virginia	Analysis of project which provided contraceptive services to married women aged 15 to 44 of high parity, before enlisting in project	1,319	13		36
1974	Kores	6 Condoms were used per mo. 33% use adjunct methods, mainly rhythm.	735	67		12.5

SOURCE: (5, P. 33), except for the 1974 Koren study which is written by Kim, E. I., Cho, N.H., Park, S. H. A follow-up survey on condom users under National Family Planning Program. Korean Institute for Family Planning, 77 P. 1974.

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APPENDIX 1

Instructions on the use of Neo Sampoon

1. Wet the tablet with a little water or with saliva; hold it between forefinger and the middle finger; insert it gradually into the vaginal.

2. Continue pushing it inwards until you touch the end of the tablet with only the forefinger. It is important to insert the tablet deep inside the vagina where the sperm will be pooled.

3. Insert the tablet 2 to 10 minutes prior to intercourse.

4. Insert a new tablet when intercourse is repeated.

Source: Adapted from Eisai Neo Sampoon brochure NSP-X--SE-032

APPENDIX 2-1

SUMMARY OF THE EVALUATION OF THE EFFECTIVENESS AND SAFETY OF MENFEGOL CONDUCTED BY EISAI RESEARCH LABORATORIES, EISAI LTD.

*

Menfegol (TS-88) is a non-ionic surfactant developed by Eisai Ltd. It has been marketed in Japan since 1969 as the spermicidal ingredient in NEO-SAMPOON Loop Tablets, a foaming vaginal contraceptive tablet.

In vitro efficacy studies, conducted by Eisai, demonstrated that Menfegol possesses potent spermicidal activity against human sperm. Menfegol was also found to immobilize Sea Urchin sperm and to block the ability of Sea Urchin and Killifish sperm to fertilize eggs.

Menfegol (in NEO-SAMPOON Loop Tablets) has been clinically evaluated in seven studies conducted by Eisai. The studies involved from 56 to 475 women and ranged from 546 to 8,955 cycles. The uncorrected pregnancy rates observed ranged from 2.3 to 7.7 pregnancies per 100 women years. The overall uncorrected pregnancy rate in all seven studies may be estimated to be 4.5. It should be noted that each clinical investigator reported that a number of the pregnancies were related to user failure rather than method failure. In each clinical study (in which a comparison was made), the pregnancy rate was reported to markedly decrease during the period in which NEO-SAMPOON Loop Tablets was used compared to the same period just prior to the use of the foaming tablet.

No serious side-effects were reported in any of the clinical studies conducted by Eisai. The most common side-effect reported was a subjective sensation of warmth in the vagina, which was considered by some women to be uncomfortable, but pleasurable by others. The tablet was reported to have no effect on vaginal cytology or cleanliness.

Menfegol is marketed at a dose-level of 60 mg in NEO-SAMPOON Loop Tablets. Assuming an average weight women as 50-60 kg, the maximum human exposure per use would be approximately 1 mg/kg. Drug Safety studies were conducted by Eisai which evaluated the toxicity of Menfegol in laboratory animals.

The acute toxicity of Menfegol was studied in mice, rats, rabbits and dogs after single intravenous, subcutaneous and oral administration. The LD50's, tabulated below, demonstrate at least a 50 fold safety margin when compared to the human intravaginal dose-level of 1 mg/kg:

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* Source: Evaluation of the Effectiveness and saffety of Menfegol as a Spermicidal Ingredient in a Vaginal Contraceptive Foaming Tablet/ Conducted by Eisai Research Lab. Submitted by Ortho Pharmaceutical corp.

APPENDIX 2-2

LD50 mg/kg (judged after 6 to 14 days)

Animal	Sex	Route of administration		
		I.V.	S.C.	P.O.
Mouse	♂	162	628	3740
	♀	195	620	3750
Rat	♂	55.5	3540	2500
	♀	67	3480	2850
Rabbit	♂	50:1/1 20:3/5 10:0/2		2000:2/3 1000:1/2 500:0/2
Dog	♂		1000:1/2	1000:0/3
	♀		500:0/2	500:0/1

A subacute (three month) toxicity study was conducted at 12.5 and 50 mg/kg in female rats using the intravaginal route of administration. There were no effects of Menfegol reported on weight gain or general symptoms of the animals. There were no effects reported on the weight or histology of major organs.

A chronic (six month) toxicity study was conducted at 0.3, 3, 30 mg/kg in female rats using the subcutaneous route of administration. With the exception of induration at the injection site at the highest dose-level, there were no drug related effects reported. Furthermore, there was little or no effect of Menfegol on general symptoms, body weight, weights of major organs at necropsy, or biochemical parameters measured. Histopathologic examination revealed no changes in the 0.3 or 3 mg/kg dose-groups; the only change in the 30 mg/kg dose-group was some liver congestion.

Teratology studies were conducted at 30, 100, 200, and 300 mg/kg in pregnant rats and mice, using the subcutaneous route of administration. The 30 mg/kg dose-level was reported to have no effects on the fetus, neonate or pregnant female of either species. At higher dose-levels, dose-related material toxicity and mortality was reported for both species. At dose-levels of 100 mg/kg or below, no effects on fetal development were reported, although this dose produced symptoms of maternal toxicity. At higher doses, fetal mortality and a low incidence of fetal anomalies were reported associated with the maternal toxicity and mortality. The investigators concluded that fetuses and newborn animals are not adversely effected by Menfegol at parenteral doses which do not produce toxic symptoms in the pregnant females.

A variety of pharmacological studies were conducted by Eisai to further characterize the safety of Menfegol. Their reports may be briefly summarized as follows:

Oral administration of 1000 mg/kg of Menfegol to rabbits resulted in gradual decrease in rectal temperature, but 100 mg/kg did not effect body temperature. Intravenous injection of 8-16 mg/kg Menfegol to cats had little effect on the spontaneous electroencephalogram.

Intravenous administration of 1-10 mg/kg of Menfegol to anesthetized dogs caused transient hypotension, increased respiration rate, and bradycardia. However, oral administration of 1000 mg/kg of Menfegol had no effect on respiration, blood pressure or electrocardiogram. Menfegol did not exhibit the histamine releasing action commonly associated with certain types of surface active agents. Menfegol had a peripheral vasodilating action when administered IV to dogs. Intravenous administration of 2 mg/kg Menfegol to anesthetized dogs produced no effect on renal function. Menfegol had no effect on the contractility of guinea pig isolated right auricle tissue when placed in tissue bath at a concentration of 1×10^{-6} g/ml.

Menfegol, at a concentration of 1×10^{-7} g/ml, produced slight contraction of isolated gastrointestinal tracts of the rat, guinea pig and rabbit, but it produced slight relaxation at 1×10^{-6} g/ml. Menfegol produced a temporary reduction in gastrointestinal motility after IV administration of 3-9 mg/kg to anesthetized dogs.

Menfegol produced no effects on the contractility of isolated uterus or spermatic duct of the rat, guinea pig or rabbit.

Menfegol caused in vitro hemolysis of rabbit and dog blood at concentrations of 0.0125 and 0.0063 percent, respectively. However, oral administration of 1000 mg/kg or subcutaneous administration of 200 mg/kg to rabbits did not result in hemolysis. Intravenous administration of 2.8 mg/kg caused a transient hemolysis in about 2-3 percent of the red blood cells.

A 5 percent solution of Menfegol caused slight depression of corneal reflex, and slight edema, when placed in the conjunctival sac, but light reflex was uneffected.

The evaluation of Menfegol, conducted by Eisai Ltd., demonstrates the in vitro spermicidal action of the compound, and its clinical effectiveness when formulated as a foaming vaginal contraceptive tablet (containing 60 mg of drug). Drug safety studies support the safety of Menfegol as a vaginal contraceptive or in the case of accidental oral ingestion.

APPENDIX 3-1

COMPARISONS BETWEEN NEO SAMPOON LOOP AND DISC TABLETS

	TABLET SIZE	TABLET WEIGHT	POTENCY	pH	EFFERVES-CENCE VOLUME	DISINTE-GRATION	SANDER-CRAMER SPERMICIDE POTENCY*
NEO-SAMPOON LOOP TABLETS	11/32"	800mg	60mg	5.9**	22mls	3.5 min.	3.6mg/ml
NEO-SAMPOON DISC TABLETS	11/32"	800mg	60mg	5.9**	21mls	3.5 min.	1.9mg/ml

* Lowest amount of formulation in 1.0ml saline that when mixed with 0.2ml human semen, results in cessation of sperm mobility in less than 20 seconds.

** Neo-Sampoon pH specifications 5-7.5

SOURCE: Evaluation of the Effectiveness and Safety of Menfegol as a Spermicidal Ingredient in a Vaginal Contraceptive Foaming Tablet. Conducted by Eisai Research Lab., Submitted by Ortho Pharmaceutical Corp.

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2. STABILITY TEST

In both Multi-dose Packaging (Aluminium Tube) and Single-dose Packaging (Aluminium Foil) same good stability was obtained. Following tables give the stability test results for both type of Packagings:

Table I Multi-dose Packaging (Aluminium Tube)
Neo-Sampoon Loop Tablets

Lot Number	Condition of Storage	Content of Menfegol	pH	Effer-vescence Volume	Disinteg-ration	Spermici-dal test
481219	Initial value	100.2%	6.6	21 ml.	3.5 min.	Passed
	3 month R.T.	100.5	6.5	21	3.5	Passed
	3 month 45°	100.3	6.4	22	3.5	Passed
	6 month R.T.	99.8	6.6	21	4.0	Passed
	12 month R.T.	100.6	6.4	22	3.5	Passed
	18 month R.T.	100.6	6.4	22	3.5	Passed
	24 month R.T.	100.8	6.6	23	3.5	Passed
	30 month R.T.	100.2	6.6	23	3.5	Passed
	36 month R.T.	100.5	6.4	21	4.0	Passed
481220	Initial value	100.0	7.0	22	3.5	Passed
	3 month R.T.	99.7	6.8	21	3.0	Passed
	3 month 45°	99.6	6.8	22	3.5	Passed
	6 month R.T.	98.8	7.0	22	3.0	Passed
	12 month R.T.	100.3	6.6	20	3.5	Passed
	18 month R.T.	100.2	6.8	22	3.5	Passed
	24 month R.T.	100.6	6.8	22	3.0	Passed
	30 month R.T.	100.6	7.0	23	3.5	Passed
	36 month R.T.	100.5	7.0	22	3.0	Passed
490100	Initial value	100.7	7.0	20	3.0	Passed
	3 month R.T.	101.3	6.8	23	3.5	Passed
	3 month 45°	100.3	7.0	22	3.0	Passed
	6 month R.T.	100.4	6.8	21	3.0	Passed
	12 month R.T.	100.9	6.6	21	3.5	Passed
	18 month R.T.	100.7	7.0	20	3.0	Passed
	24 month R.T.	100.1	6.8	22	4.0	Passed
	30 month R.T.	100.0	6.8	23	3.5	Passed
	36 month R.T.	100.8	7.0	20	3.5	Passed

R.T. = Room temperature

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Table II Single-dose Packaging (Aluminium Foil)
Neo-Sampoon Disc Tablets

Lot Number	Condition of Storage	Content of Menfegol	pH	Effer-vescence Volume	Disinteg-ration	Spermici-dal test
500226	Initial value	100.3%	6.4	22 ml.	3.5 min.	Passed
	3 month R.T.	99.7	6.6	24	4.0	Passed
	3 month 45°	100.0	6.5	23	4.0	Passed
	6 month R.T.	100.2	6.4	24	3.0	Passed
	12 month R.T.	99.8	6.6	23	4.5	Passed
	24 month R.T.	99.9	6.6	23	4.5	Passed
500324	Initial value	98.7	6.4	23	3.5	Passed
	3 month R.T.	98.4	6.4	24	3.5	Passed
	3 month 45°	98.8	6.4	24	4.0	Passed
	6 month R.T.	98.7	6.4	22	3.5	Passed
	12 month R.T.	98.8	6.6	23	3.0	Passed
	24 month R.T.	98.7	6.6	24	3.5	Passed
500307	Initial value	99.3	6.4	22	3.5	Passed
	3 month R.T.	99.2	6.4	25	3.5	Passed
	3 month 45°	99.1	6.4	23	4.0	Passed
	6 month R.T.	99.4	6.4	24	4.0	Passed
	12 month R.T.	99.4	6.4	24	3.5	Passed
	24 month R.T.	99.5	6.4	23	3.5	Passed

R.T. = Room temperature