



## ALLERGY SUPPORT

*GRAMINEX Flower Pollen Extract*

# Flower Pollen Extract and its Effect on Allergies

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## Assessment of Sensitizing Potential

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2060 Cernitin T60

2065 Cernitin GBX

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### INTRODUCTION

A combination of 2060 CERNITIN T 60 and 2065 CERNITIN GBX was found to be sensitizing in guinea pigs when tested according to the maximization method of Magnusson and Kligman (1). In this test, a 5% suspension of CERNITIN T 60 and CERNITIN GBX (60 + 3) was administered intracutaneously together with complete Freund adjuvant, followed after 7 days by an epidermal application of a 25% suspension of the test substance combination. Two weeks after the induction exposure, the animals were challenged by a further topical application of the same suspension. They revealed a positive reaction.

Thus, the maximization procedure demonstrated an allergenic potential or sensitizing capacity of the test material, without however indicating an actual risk of sensitization in man.

In order to interpret the experimental finding it is important to realize that the guinea pig maximization test is a diagnostic procedure for predicting delayed-type sensitivity to proteins and soluble antigen-antibody complexes on the skin. The cell-mediated reaction produces contact dermatitis and other allergies of the tuberculin-type. However, allergens associated with pollens induce immediate-type reactions which are associated

with circulating antibodies of the IgE class. Allergens of this sort are capable of inducing hay fever, bronchial asthma, urticaria, and anaphylactic shock.

It is to be expected that water soluble protein or peptide components of CERNITIN T 60 may induce a delayed type reaction when injected intradermally with complete Freund adjuvant as immune enhancer. The relevance of the laboratory procedure as it was performed is however limited as it does not apply to the practical use conditions of the CERNITIN extracts of pollens. Since the therapeutic use is oral rather than topical, it is more appropriate to rely on information of occupational exposure and of side effects in patients in order to assess the risk of allergic reactions. Atopic patients may be considered to be at particular risk of developing allergic disorders. Such individuals were subjected to immunotherapy with high doses of CERNILTON in order to achieve desensitization upon oral treatment.

### MEDICAL ASSESSMENT

#### Occupational Exposure

No symptoms suggestive of pollen allergies have been reported over 5 years in personnel engaged in production of the pollen extracts CERNITIN T 60 and GBX (2).

### Adverse Effects During Therapy of Benign Prostatic Hyperplasia

Controlled clinical studies confirmed the good tolerability of CERNILTON N. In a study conducted over 24 weeks, 3 patients out of 92 treated reported gastrointestinal side effects (3). A similar incidence (4%) occurred in an open study which involved 1798 patients treated for 24 weeks (2 tablets 100 mg t.i.d.) (4).

During 1984-1991 (sales volume 145'801'000 tablets CERNILTON/CERNILTON N), post-marketing surveillance in Germany resulted in 113 reports of adverse effects. The large majority (96 cases) consisted of gastrointestinal disturbances, 10 developed a variety of cutaneous symptoms and only 2 developed "allergy" of a non-specified nature (5).

By contrast, no reports on side effects of CERNILTON/ADRENOPROSTAL were received in Switzerland (6), or in Korea of CERNILTON tablets sold since 1975 (7), or in Japan where CERNILTON is marketed since 1969 (8). Likewise, no side effects are reported in Argentina (sales volume > 150 million CERNILTON tablets since 1975) (9), or in Austria (> 8 000'000 CERNILTON/PROSTAFLO tablets sold since 1983) (10).

### Tolerance Study in Patients with Pollen Allergy

Twenty eight patients (18 men and 10 women) suffering from seasonal allergic rhinitis (pollinosis) received 4 daily capsules of STHENOREX (120 mg T60 and 6 mg GBX per capsule) at intervals, including the pollen season. Although the skin test to STHENOREX was positive, no reaction to oral treatment was observed and there was no improvement of the allergic condition. (11).

### Immunotherapy

In an open study in Switzerland, 44 patients suffering from seasonal allergic rhinitis were treated for 2 months with daily doses of 840 mg T60 and 42 mg GBX (one FH 84 sachet), or 1680 mg T60 and 84 mg GBX ( 2 sachets), respectively. This amount is equal to 4.5 to 9 times the usual daily dose of CERNILTON. Apart that the treatment was considered effective in 70% of the patients, there were no untoward allergic reactions, or other side effects (12).

A similar study was carried out in Argentina on a total of 47 patients who received one or two sachets of FH 84, or placebo. Apart from one patient each who experienced transient diarrhea or

sinusitis, treatment was uneventful (therapeutic effects due to FH 84 could not be ascertained as other drugs with antiallergic properties were administered) (12).

A double-blind, placebo controlled study was performed in Italy (13). Thirty four pollinosis patients received 2 sachets of FH 84 for 30 days, and 41 matching patients the placebo only. There was no overall significant effect of treatment and no side effects were encountered.

### CONCLUSION

The vast clinical experience indicates that CERNITIN T 60 and CERNITIN GBX are well tolerated. Side effects are rare and generally limited to the gastrointestinal tract. Reactions reminiscent of allergic effects have been reported in single cases only.

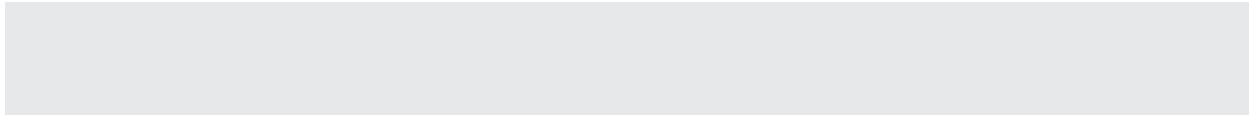
It is concluded that the standardized CERNITIN extract of pollen is devoid of allergenic properties when administered by the oral route. This has amply been demonstrated in therapeutic use as well as in special studies involving high dosage in atopic patients.

Robert Hess, M.D.

Date: November 3, 1992

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## Double-Blind , Comparative, Clinical Study of the FH 84 and Placebo in Patients with Hay Fever

1989

### 1. Aim of the study

The aim of the single-centre, double-blind study was to compare the efficacy of a product containing standardized pollen extracts (FH 84) versus a placebo in patients with hay fever.

### 2. Patients and methods

The double-blind study was carried out in one hospital (Ospedale Maggiore Niguarda, Milan/Italy) under the supervision of Prof. Dr. C. Ortolani.

There have been two patient groups:

- The FH 84 group which received the pollen extracts (34 patients)
- The placebo group which received a non active component (41 patients)

The patients have been randomized to the two groups according a provided randomization list.

The structural homogeneity of the two groups in regard to the concomitant factors (age, sex, weather, wind) was assured.

The pollen extracts as well as the placebo have been given in powder form. The powders were filled in sachets and the patients had to take twice a day one sachet. A sachet with FH 84 contained 840 mg of a water soluble pollen extract (Cernitin T60), 42 mg of a fat soluble pollen extract (Cernitin GBX) and inactive ingredients ad 3000 mg.

A sachet with placebo contained 3000 mg inactive ingredients.

The patients received sachets for 30 days together with a form where they had to report daily their symptoms. The following symptoms were considered for the double-blind study:

- Ocular symptoms (itching, redness, and lacrimation)
- Nasal symptoms (sneezing, running nose and blocked nose)
- Pulmonary symptoms (asthma, dyspnoea and cough)

Every patient had to assess himself the symptoms by means of valuation scale:

0 = symptoms not present

1 = slight symptoms

2 = moderate symptoms

3 = severe symptoms

The statistical evaluation has been carried out by a simple data description and by the z-test for comparison of the mean values of two very large random samples. In the statistical tests the unilateral alternative hypothesis that the FH 84 treatment acts better than placebo was laid down.

### 3. Results

For the ocular symptoms, itching, redness and lacrimation, it can be demonstrated that under the treatment with FH 84 the mean intensity was lower than under placebo. The differences ranged from a trend to slight statistical significance ( $0.04 < p < 0.10$ ). Here, considered globally, a slightly significantly better efficacy of the FH 84 treatment was thus to be observed.

For the nasal symptoms, sneezing, running nose and blocked nose, no better efficacy was observed under the treatment with FH 84 ( $p > 0.45$ ).

For the pulmonary symptoms, asthma, dyspnoea and cough, a slight trend can perhaps be recognized for a somewhat better effect with FH 84 than with placebo ( $0.05 < p < 0.15$ ).

During the whole study no patient of the two groups showed side effects. FH 84 as well as placebo have been very well tolerated.

## **FH 84 IN ALLERGIC RHINITIS**

**1990**

However it seems, a statistical evaluation has not been done, that FH 84 had an additive effect when given together with other antiallergic agents.

In Italy a double-blind clinical study has been carried out in 1988. The first group (34 patients) received two sachets with FH 84 daily. The second group (41 patients) received two sachets with a placebo powder daily.

The efficacy of FH 84 and placebo on the following symptoms had to be observed:

- Ocular symptoms (itching, redness and lacrimation)
- Nasal symptoms (sneezing, running nose and blocked nose)
- Pulmonary symptoms (asthma, dyspnoea and cough)

There has been observed a slightly significantly better efficacy of FH 84 concerning the ocular symptoms whereas no better efficacy has been seen for the nasal symptoms. For the pulmonary symptoms a slight trend of a better efficacy with FH 84 than placebo has been found.

### **FH 84**

FH 84 is a product containing standardized pollen extracts. FH 84 is used in the treatment of allergic rhinitis above all against hay fever.

FH 84 is presented in sachets of 3 grams and has the following composition:

- Cernitin T60  
(water-soluble pollen extract)  
840 mg
- Cernitin GBX

(fat-soluble pollen extract)

42 mg

- Inactive ingredients ad  
3000 mg

Dosage: Twice a day 1 to 2 sachets in half a glass water

Side effects and contraindications: Have not been reported up to now.

### **Clinical studies with FH 84**

In Switzerland (Tessin) in 1985 and 1986 44 patients with hay fever have been treated with FH 84. The patients have received 1-2 sachets with FH 84 daily.

A very good efficacy of FH 84 treatment has been observed in 6 patients (13.6%), a good efficacy in 15 patients (34%), a moderate efficacy in 10 patients (22.7%) and an insufficient efficacy in 13 patients (29.6%).

In Argentina a clinical study has been carried out in 1986 with three groups of patients.

The first group (17 patients) received one sachet with FH 84 a day. The second group (10 patients) received two sachets with FH 84 a day and to the third group (20 patients) was given daily one sachet with placebo.

Most of the patients of all three groups were treated besides the test substances (FH 84 or placebo) with other antiallergic agents. For this reason it must be said that the mostly good effects of the treatment have not been exclusively the result of FH 84 treatment.

## Results of an open clinical trial with FH84 (Cernitin Pollen Extract) in patients with Pollinosis.

Mazzi Rodolfo, Lugano, Switzerland (1986).

### ***Aim of trial***

To evaluate the effect of FH84 in patients, who are allergic to flower pollen and suffering from pollinosis. The trial should provide information on the improvement concerning the symptoms (mainly Rhinitis and Conjunctivitis) and on the occurrence of adverse (allergic) reactions. The patients have been treated in 4 centers.

<b><i>Principal Investigator</i></b>	Dr. R. Mazzi, Locarno, CH	Center 1
<b><i>Co- Investigators</i></b>	Dr. G. Bolognini, Mendrisio, CH	Center 2
	Dr. S. Gilardi, Locarno, CH	Center 3
	Dr. T. Pani, Lugano, CH	Center 4
<b><i>Sponsors</i></b>	Cernitin SA, Lugano, CH	
	Lagap SA, Lugano, CH	
<b><i>Dosage</i></b>	1-2 sachets of FH84/day corresponding to 840mg T60 and 42mg GBX/sachet (1 sachet = 3g)	
<b><i>Period of treatment</i></b>	March- July 1985 and 1986 respectively	

### ***Summary***

FH84 taken prophylactically in early spring has caused a positive response in 66% of a collective of 45 patients suffering from pollinosis. The patients have reported of an improvement of symptoms, especially concerning Rhinitis, Conjunctivitis and Sneezing. Age and sex of the patients did not significantly influence the result of the treatment. The date of start of treatment, whether March or April did not influence the results. There seemed to be a clear dose/response relation. Patients treated with 2 sachets per day form by far the best group with only "good" or "completely disappeared" results. No adverse reactions have been observed. Even a high dosage of FH84 (up to 1.6 gram of Cernitin Pollen Extract) administered per os did not cause allergies patients usually highly allergic to flower pollen.

### ***Introduction***

FH 84 contains as active ingredient a flower pollen extract, which is standardized in composition and production process (called: Cernitin Pollen Extract). During the spring of 1985 and 1986 respectively, 45 patients suffering from Pollinosis have been treated with FH84 prophylactically to evaluate the effect of the drug on the symptoms of Pollinosis. An additional aim of the trial has been to evaluate the tolerability of the Cernitin Pollen Extract, given per os at a high dosage to patients, known to be allergic against flower pollen.

FH84 is presented in powder form in aluminum sachets and has been administered daily per os (1 or 2 sachets). Each sachet contains 3g of FH84, which corresponds to 882 mg of Cernitin Extract {T60 (water-soluble components): 840 mg; GBX (fat-soluble components): 42 mg}.

The patients have been treated in 4 centers in Lugano and Locarno in the southern part of Switzerland. The trial has been carried out as an open trial. For each patient a detailed Case Record Form has been worked out and completed by the investigator(s).

### Centers and Patients

The following 4 physicians participated in the trial:

Center 1: Dr. R. Mazzi, Locarno (CH) (Principal Investigator)

Center 2: Dr. G. Bolognini, Mendrisio (CH)

Center 3: Dr. S. Gilardi, Locarno (CH)

Center 4: Dr. T. Pani, Lugano (CH)

The patients have been divided as follows:

*Table 1: Distribution of patients according to centers, sex and age.*

	Center	1	2	3	4	Total
	<b>Number of patients</b>	22	13	5	5	45
<b>Sex:</b>	<b>Men</b>	10	9	3	4	26
	<b>Women</b>	12	4	2	1	19
<b>Age:</b>	<b>Under 25</b>	7*	5	2	3	17
	<b>Over 25</b>	7*	8	3	2	20

\* for 8 patients of center 1 (1985) data on age are missing

### Dosage

The normal dosage has been 1 sachet of FH84 per day. In center 2 however, 7 patients out of 13 have been treated with a double dose of 2 sachets daily.

### Results

The results of the treatment have been evaluated in two ways:

a) Effect of the treatment on the following of pollinosis:

- Pruritis
- Sneeze
- Rhinitis
- Conjunctivitis
- Asthma

The patient had to report on each symptom whether at the end of the treatment it has:

- completely disappeared
- much improvement
- moderately improved
- remained unchanged
- deteriorated

b) General assessment of the treatment:

the patient and the physician had to judge each one separately, whether the result of the treatment has been considered as

- very good
- good
- mediocre
- non-satisfactory

#### 4.1 Effect of FH84 on the symptoms of pollinosis

*Table 2: Combined results 1985/86, 45 patients (figures are number of patients)*

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
<b>completely disappeared</b>	4	7	4	7	4
<b>much improved</b>	3	11	16	12	4
<b>moderately improved</b>	5	9	10	9	6
<b>unchanged</b>	6	11	13	11	6
<b>deteriorated</b>	1				

A majority of patients reported moderate to substantial improvement for the symptoms of Sneeze, Rhinitis and Conjunctivitis. 66,6% of the patients reported a positive response for Rhinitis, 62,2% for Conjunctivitis and 60% for Sneeze. Much improved and/or completely disappeared were: 44,4% for Rhinitis, 42,2% for Conjunctivitis and 40% for Sneeze. Detailed data for each center are found in table 1-8 of the annex of this report. Even though the figures suggest quite a positive result for FH84, one has to consider the high placebo effect, the low number of patients and lack of statistical evaluation.

#### 4.2 General Assessment of the treatment

Data on each patient concerning age, sex, dosage, start and end of the treatment, as well as concerning the assessment of the treatment are found in table 10-13 of the annex to this report.

The combined results of all 4 centers are shown in the following table:

*Table 3: Combined results of the treatment of FH84, 1985/86, 45 patients*

Centers	1	2	3	4	Total	%
<b>Results</b>						
<b>very good</b>	2	1	-	3	6	13.3
<b>good</b>	8	9	-	1	18	40.0
<b>mediocre</b>	5	1	-	1	7	15.6
<b>non-satisfactory</b>	7	2	5	-	14	31.1
<b>adverse effects</b>	0	0	0	0	0	0

68.9% of the patients responded positively to the drug. Good to very good response has been achieved by 53.3%. Over 15% showed a mediocre result and 31.1% did not respond at all.

#### 4.3 Adverse Reactions to FH84

It is remarkable to notice that no adverse reactions (allergies) have been observed or reported due to the treatment with Cernitin Pollen Extract. One has to recall the high dosage of Pollen Extract in FH84 (corresponding to more than 10 tablets Cernilton/day) and the sensitivity of the special selected patients, who are generally allergic to flower pollen. From the present trial can be concluded, that per os intake of Cernilton Extract up to 882 mg/day do not cause any allergic reactions. 7 patients of center 2 have been treated with 1764 mg/day and did not show adverse reactions.

#### 4.4 Effect of the treatment in function of the genus

The following table shows that there is no substantial difference concerning the sex, except that the assessment of "very good" is rarer in the groups of women.

*Table 5:*

	Number of Patients		% of patients	
	M	F	M	F
<b>Total of patients</b>	26	19	100	100
<b>Results:</b>				
<b>Very good</b>	5	1	19.2	5.3
<b>Good</b>	10	8	38.5	42.1
<b>Mediocre</b>	4	3	15.4	15.8
<b>Non satisfactory</b>	7	7	26.9	36.8

#### 4.5 Effect of treatment in function of age

*Table 6:*

	Number of patients		% of patients	
	Under 25	Over 25	Under 25	Over 25
<b>Total of patients</b>	17	20	100	100
<b>Results:</b>				
<b>Very good</b>	3	2	17.6	10.0
<b>Good</b>	6	9	35.4	45.0

<b>Mediocre</b>	4	1	23.5	5.0
<b>Non satisfactory</b>	4	8	23.5	40.0

The only surprising difference is in the “mediocre” group, where under 25 years of age there is a percentage of 23.5%, but over 25 years only 5%. It seems that many of the over 25 years patients simply judge a mediocre result as “non satisfactory”.

#### 4.6 Effect of treatment in function of dosage

The results of center 2 (see table 11 of annex) clearly show a much more consistent and better result by taking 2 sachets instead of 1 per day. All 7 patients report good to very good results. Such a result has not been observed in any other group or center.

#### 4.7 Start/end of treatment

The date of start or duration of the treatment did not influence the results.

### 5. Conclusions

#### 5.1 Efficacy

The prophylactic intake of FH84 in spring has caused a certain relief in the symptoms of patients suffering from pollinosis. Over 65% of the 45 patients reported of an improvement of their conditions at the end of the treatment, especially concerning the symptoms of Rhinitis, Conjunctivitis and Sneezes.

In this preliminary, open study no difference has been observed regarding sex and age of the patients. Also, the beginning of the treatment, whether March or April, seemed not to have any influence on the results. However, a treatment with a double dose (2 sachets/day) definitely improved the outcome of the treatment. The present results have not been statistically analyzed. One has to take into consideration the low number of patients and the high placebo effects, as well as the varying weather conditions. A final conclusion concerning the efficacy of the product will need a further trial with more patients and a control group ideally the trial should be blinded.

#### 5.2 Tolerability

The present study is however very convincing concerning the tolerability of FH84. At the high dosage of 882 mg of Cernitin Flower Pollen Extract there has not been observed any adverse effects, say allergies in all 38 patients receiving this dosage. Seven patients receiving 1764 mg daily did also not show any allergic reaction. Thus, the conclusion is justified, that Cernitin Pollen Extract (FH84) does not cause allergenicity when administered orally.

### ANNEX

#### Mazzi Rodolfo

#### Results of an open clinical trial with FH84

#### (Cernitin Pollen Extract)

#### in patients with Pollinosis (1986)

1. Data on single patients and evaluation of the therapy for each patient
2. Effect of FH84 on the symptoms  
(Pruritis, Sneezes, Rhinitis, Conjunctivitis and Asthma)

Table 1-9

Dr. R. Mazzi, Center 1

Patient Number	Initials	Sex	Age	Dosage (Sachets/d)	Start	End	Adverse Reactions	RESULTS very good	RESULTS good	RESULTS mediocre	RESULTS non-satisfactory
1985											
1	P.F.	M	-	1	01.06.	01.07.	none	X			
2	C.A.	M	-	1	15.03.	01.07.	stomach		X		

3	A.R.	M	-	1	15.03.	01.07.	none	-*	-*	-*	-*
4	L.G.	M	-	1	15.03.	01.07.	none			X	
5	G.N.	F	-	1	15.04.	15.06.	none		X		
6	A.M.	M	-	1	15.01.	15.06.	none			X	
7	Z.G.	F	-	1	01.05.	31.05.	none		X		
8	A.A.	F	-	1	01.05.	15.06.	none				X
9	P.P.	F	-	1	01.05.	15.06.	none				X
<b>1986</b>											
1	P.E.	F	47	1	20.03.	03.08.	none				X
2	C.N.	M	16	1	20.03.	03.08.	none			X	
3	D.M.	F	19	1	18.03.	30.05.	none				X
4	P.G.	F	42	1	01.04.	26.07.	none			X	
5	A.R.	M	21	1	01.04.	15.06.	none	X			
6	K.D.	M	21	1	15.03.	15.04.	none	(X)	X		
7	B.Q.	M	40	1	01.04.	16.06.	none				X
8	S.C.	F	46	1	02.04.	16.06.	none		X		
9	I.R.	F	45	1	01.04.	04.06.	none				X
10	W.S.	F	26	1	30.04.	31.07.	none		X		
11	M.M.	F	15	1	08.04.	29.06.	none			X	
12	Z.G.	F	43	1	01.03.	30.06.	none	(X)	X		
13	D.G.C.	M	20	1	08.04.	08.07.	none		X		
14	E.U.	M	20	1	15.04.	15.06.	ECZ. ?**				X

\* results not recorded (eliminated from final evaluation)

\*\* irritation of pre-existing eczema (hands); objectively doubtful.

### Dr. G. Bolognini, Center 2

Number	Initials	Sex	Age	Dosage (Sachets/d)	Start	End	Adverse Reactions	RESULTS very good	RESULTS good	RESULTS mediocre	RESULTS non-satisfactory
<b>1985</b>											
1	C.M.	M	24	1	26.03.	03.05.	none		X		
2	G.P.	M	38	1	01.03.	30.05.	none				X
3	C.N.	F	41	1	28.02.	30.05.	none		X		
4	S.E.	M	42	1	04.03.	30.05.	none		X		
5	M.L.	M	35	1	23.03.	30.05.	none				X
6	B.M.	F	19	1	26.03.	19.06.	none			X	
<b>1986</b>											
1	N.B.	M	48	2	01.03.	31.05.	none		X		
2	C.N.	F	42	2	15.03.	15.06.	none		X		
3	V.G.	M	22	2	15.03.	15.07.	none	X			
4	B.M.	M	38	2	01.02.	01.06.	none		X		
5	B.M.	F	20	2	15.03.	30.05.	none		X		
6	M.A.	M	27	2	15.03.	30.06.	none		X		
7	C.M.	M	24	2	14.03.	30.06.	none		X		

### Dr. S. Gilardi, Center 3

Patient Numbers	Initials	Sex	Age	Dosage (Sachets/d)	Start	End	Adverse Reactions	RESULTS very good	RESULTS good	RESULTS mediocre	RESULTS non-satisfactory
<b>1986</b>											
1	B.S.	M	34	1	29.03.	19.06.	none				X
2	S.J.	F	37	1	15.05.	05.07.	none				X
3	B.E.	M	47	1	15.04.	20.08.	none				X
4	B.B.	F	16	1	07.04.	20.08.	none				X
5	C.G.	M	16	1	15.04.	28.08.	none				X

### Dr. T. Pani, Center 4

Patient Numbers	Initials	Sex	Age	Dosage (Sachets/d)	Start	End	Adverse Reactions	RESULTS very good	RESULTS good	RESULTS mediocre	RESULTS non-satisfactory
<b>1986</b>											
1	L.F.	M	30	1	24.02.	22.04.	none	X			
2	N.G.	F	54	1	13.03.	30.04.	none	X			

3	S.M.	M	20	1 (1.5.:2)	01.04.	23.05.	none			X	
4	S.L.	M	17	1	14.04.	30.05.	none		X		
5	M.S.	M	16	1	15.04.	13.05.	none	X			

**Table 1: Results of Center 1, 1985, 8 patients (Dr. R. Mazzi)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared			1	1	
much improved		2	1	1	
moderately improved		3	3	2	1
unchanged		2	2	1	1
deteriorated					

**Table 2: Results of Center 1, 1986, 14 patients (Dr. R. Mazzi)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared	3			2	2
much improved	1	5	5	2	1
moderately improved	4	5	3	4	
unchanged	1	4	5	5	1
deteriorated	1				

**Table 3: Combined results of Center 1, 1985 and 1986, 22 patients**

**(Dr. R. Mazzi)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared	3		1	3	2
much improved	1	7	6	3	1
moderately improved	4	8	6	6	1
unchanged	1	6	7	6	2
deteriorated					

**Table 4: Results of Center 2, 1985, 6 patients (Dr. G. Bolognini)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared					1
much improved			3	3	1
moderately improved			1	1	1
unchanged			2	2	
deteriorated					

**Table 5: Results of Center 2, 1986, 7 patients (Dr. G. Bolognini)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared		2			
much improved	1	4	5	5	2
moderately improved		1	2	2	4
unchanged					
deteriorated					

**Table 6: Combined results of Center 2, 1985 and 1986, 13 patients**

**(Dr. G. Bolognini)**

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared		2			1
much improved	1	4	8	8	3
moderately improved		1	3	3	5
unchanged			2	2	

deteriorated					
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Table 7: Results of Center 3, 1986, 5 patients (Dr. S. Gilardi)

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared		1	1		
much improved					
moderately improved					
unchanged	5	4	4	3	4
deteriorated					

Table 8: Results of Center 4, 1986, 5 patients (Dr. T. Pani)

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared	1	4	2	4	1
much improved	1		2	1	
moderately improved	1		1		
unchanged		1			
deteriorated					

Table 9: Combined results of all 4 Centers 1985 and 1986, 45 patients

	Pruritis	Sneeze	Rhinitis	Conjunct.	Asthma
completely disappeared	4	7	4	7	4
much improved	3	11	16	12	4
moderately improved	5	9	10	9	6
unchanged	6	11	13	11	6
deteriorated	1				

## Results.

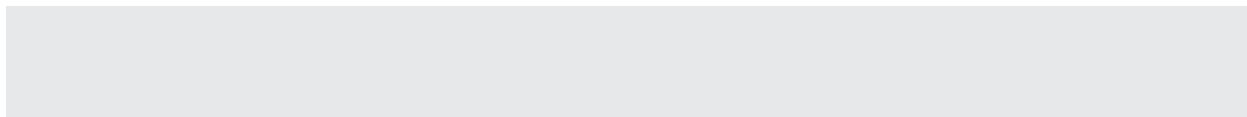
% Inhibition (=100-(inhibit/uninhibit) x100)

Konc.	T60, ZB 207	T60, ZB 208	Timothy	Konc.
5 mg/ml	0	4,5	94,1	100.000 SQ/ml
$5 \times 10^{-1}$ mg/ml	0	0	90,1	10.000 SQ/ml
$5 \times 10^{-2}$ mg/ml	5,5	3,2	76,8	1000S Q/ml
$5 \times 10^{-3}$ mg/ml	0,7	0	0	100 SQ/ml
$5 \times 10^{-4}$ mg/ml	7,2	0,2	0	10 SQ/ml
$5 \times 10^{-5}$ mg/ml	2,3	12,5	0	1 SQ/ml

(Encl. 1)

## CONCLUSION

Using the Maxi-RAST inhibition system it is shown, that neither of the two extracts were able to inhibit the response of the patient 50% or more, which is the criterion for a positive response. Inhibition below 20% is considered an unspecific reaction.



## Study of Tolerance of the Stheborex in Patients with Pollen Allergy

Dr. GARCELON

The term pollen allergy covers the totality of pathological processes that occur when pollen grains come into contact with the conjunctival and respiratory mucosa of specifically sensitized individuals. But what happens if the contact takes place with a different mucosal surface, such as that of the digestive tract?

This is the question that one is entitled to ask in relation to the drug STHENOREX, an appetite-stimulant drug composed of water-soluble and lipid-soluble extracts of pollens, comprising:

- 2 species of tree pollen: pine and alder.
- 4 species of grass pollen, viz:
  - 2 cereals: rye and maize, and
  - 2 species of hay-grasses, timothy and cocksfoot.

These extracts are contained in a 'gelule' which only releases the active compounds contained in it in the presence of gastric juice.

Research carried out several years ago by Madame VAN CAMPO, Director of Research at CARS, demonstrated the presence of numerous pollens in ordinary white bread and rye bread.

Thus:

- in 18g of ordinary white bread she found 364 grains of all kinds of pollens, representing, 20 grains of pollen per gram of bread, of which 17 were grains of cereal pollen (table A);
- in 10g of crumb of rye bread, she found 701 grains of pollen, or 70 grains per gram, of which 25 were grains of cereal pollen (table B).

Now individuals who suffer from typical pollen allergy eat bread without thereby aggravating their symptoms.

It is therefore justifiable to expect that pollen that is ingested and therefore digested, undergoes such a degree of chemical breakdown that it loses all capacity of provoking allergic reactions on the digestive mucosa.

This hypothesis, in the particular case of STHENOREX, has been completely confirmed by the clinical trial carried out by Dr. Garcelon.

We have made a search for clinical sensitivity to STHENOREX in patients consulting us for spasmodic coryza, conjunctivitis or seasonal asthma (in May, June or July), provoked by allergy to a variety of pollens.

These symptoms were present individually or in various combinations, in a total of 28 patients.

A gelule of STHENOREX contains:

- Water-soluble pollen extract  
120mg
- Lipid-soluble pollen extract  
6mg
- Base: Q.S.P.  
one gelule
- Sulphurous anhydride  
1g p. 1000

The composition of pollens contained in STHENOREX is as follows:

- PINE (Pinus montana)
- ALDER (Alnus glutinosa)
- RYE (Secale cereale)
- MAIZE (Zea mais)
- TIMOTHY (Phleum pratense)
- COCKSFOOT (Dactylis glomerata)

The 28 patients studied were distributed as follows:

- 18 males, mean age 26 (range 9 to 51),
- 10 females, mean age 25 years (range 9 to 40).

This confirms that pollen allergy is most commonly found amongst young people.

Pollen allergy can be objectively demonstrated by skin tests carried out with a control solution and

concentrated extracts prepared by the Stallergenes laboratory:

- Trees (particularly group II).
- Grasses (12 fodder grasses and 3 cereals),
- Weeds.

A number of observations were carried out using a test based on a concentrated rye-pollen extract prepared by the Pasteur Institute. In addition, one test was systematically carried out using STHENOREX powder diluted in one drop of 0.1 N sodium bicarbonate.

EXPERIMENTAL PROTOCOL

Once the diagnosis of pollen allergy had been made and skin sensitivity to one or more groups of pollens (including the dry extract of STHENOREX) had been demonstrated, the first stage of the clinical trial comprised the oral administration of one gelule of STHENOREX. The patient remained under medical supervision for three hours, so that any immediate-type allergic reaction could be demonstrated.

Once this stage had been passed uneventfully, the patient took a further four gelules daily for one week, this being the usual dosage of the drug. If no reaction was noted, treatment was re-started 15 or 30 days later, at the same dosage, so as to investigate any possible antigenicity of the product. Finally, when the preceding stages of the trial had passed without incident, STHENOREX was administered to sensitized subjects during the pollen season.

RESULTS

In 20 subjects tested, we made the following observations:

POSITIVE TESTS:

Fodder grasses: 27

(one subject being sensitized only to rye pollens),

	<u>Trees</u>
.....9	
	<u>Cereals</u>
.....24	
	<u>STHENOREX</u>
.....9	

In 20 subjects who ingested STHENOREX as described above, no reaction was seen. Treatment was perfectly tolerated, even during the pollen season (June). However, patients who had been prescribed the drug for therapeutic purposes during

this period (there were 5 of these) showed no improvement in their allergic symptoms from its use.

DISCUSSION

Apart from the sensitivity to rye pollens alone, seen in one of the subjects we studied, it is not surprising to note that allergy to grass pollens, which is a feature of most pollen allergy in the Paris region, was the predominant pattern, and was most commonly accompanied by sensitivity to cereal pollens, while the importance of tree pollens, though not negligible, was of minor degree.

The fact that one third of tests with STHENOREX powder gave a positive result demonstrates that despite the various modifications under-gone by the product in the course of manufacture (during which the allergenic polypeptide fractions are broken down to amino acids); the product retains its specific antigenic properties.

The degree of hypersensitivity varies from one individual to another, and it is worthy of note that seven of the eight patients who reacted to STHENOREX were those with the greatest number of positive reactions to the various groups of pollens studied.

Finally, even though cases of 'ultra-specificity' may be rare, (1 out of 28), certain patients may be sensitized to a single specific pollen, e.g. rye pollen, which is in fact contained in STHENOREX. Other clinical and immunobiological investigations carried out in various hospitals have also shown analogous instances of cross-antigenicity between STHENOREX and various types of pollen.

CONCLUSION

At all events, clinical tolerance of STHENOREX is excellent. Its oral administration to a group of patients with pollen allergy did not give rise to any allergic reactions. The product is not itself a sensitizer, and while it contains amino acids of vegetable origin that are capable of giving rise to positive skin tests in certain subjects, it is likely that it rapidly loses all antigenic specificity during its absorption by the digestive tract.

Dr. M. GARCELON

July

1975

