

## REFERENCES

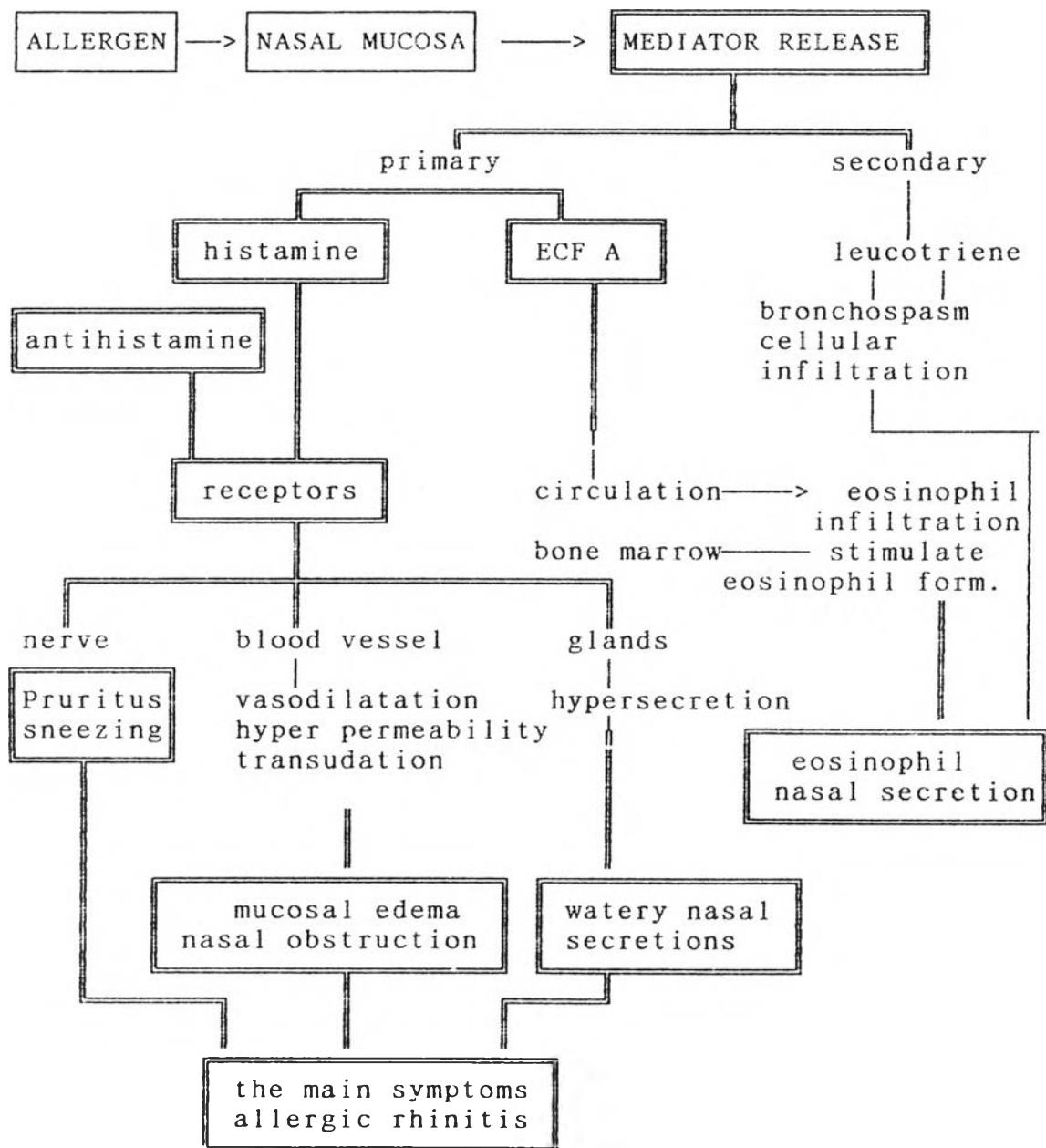
1. Kay A B. Mechanisms and treatment of allergic rhinitis in Scott-Brown's Otolaryngology Butterwarth & Co London: 1987: 93-109.
2. Nalebuff D.J. Allergic rhinitis in Otolaryngology-Head and Neck Surgery Cumming CW Mosby-Year Book Boston: 1992: 763-773.
3. Berman B.A. Perennial allergic rhinitis : Clinical efficacy of a new antihistamine J Allergy Clin Immunol 1990; 86: 1004-1008.
4. Wihl J.A., Kunkel G, Middleton E J. Perennial rhinitis in Allergic and vasomotor rhinitis: Clinical aspects Mygind N & Weeke B Workshop at Righospitalet Copenhagen: 1985: 36-39.
5. Bantz EW, Dolen WK, Chadwick EW, Nelson HS. Chronic Chlorpheniramine therapy: sub-sensitivity, drug metabolism, and compliance Annals of Allergy 1987; 59:341-45.
6. Meltzer EO. Performance effects of antihistamines J Allergy Clin Immunol 1990; 86: 613-9.
7. Mansmann HC, Altman RA, Berman BA at al. Efficacy and safety of Cetirizine therapy in perennial allergic rhinitis Annals of Allergy 1992; 68: 348-53.
8. Kemp J.F., Buckley C.E. Gershwin M.E., Buchman E.. Cascio F.L., Buchman E at al. Multicenter, double blind, placebo controlled trial of Terfenadine in seasonal allergic rhinitis and conjunctivitis Annals of Allergy 1985; 54: 502-509.
9. Weiler JM, Donnelly, Cambell BH at al. Multi center, double blind multiple dose parallel groups efficacy and safety trial of azelastine, Chlorpheniramine and placebo in the treatment of spring allergic rhinitis J Allergy Clin Immunol 1988; 82: 801-11.

10. Simons FER, Mc Millan JL, Simons KJ. A double blind, single dose, cross-over comparison of Cetirizine, Terfenadine, Loratadine, Astemizole and Chlorpheniramine versus placebo: Suppressive effect on histamine-induced wheals and flares during 24 hours in normal subject J Allergy Clin Immunol 1990; 86: 540-7.
11. Sjawitri P., Siregar, Munazir Z., Akib A., Suyoko D., Matondang C.S. Prevalensi penyakit atopik pada anak di kelurahan Utan Kayu Medika 1992; 9: 19-24.
12. Naclerio RM. The role of histamine in allergic rhinitis J Allergy Clin Immunol 1990; 86: 628-32.
13. White MV. The role of histamine in allergic diseases J Allergy Clin Immunol 1990; 86 : 599-605.
14. Simons FER, Simons KJ. Histamine and H<sub>1</sub> receptor antagonist in Textbook of Pharmacology WB Saunders Co Philadelphia; 1992: 1105- 1117.
15. Siedel WF, Cohen S, Bliwise NG, Dement WC. Cetirizine effects on objective measures of daytime sleepiness and performance Annals of Allergy 1987; 59: 58-62.
16. Simons FER. H<sub>1</sub>-receptor antagonists : Clinical pharmacology and therapeutics J Allergy Clin Immunol 1989; 84: 845-857.
17. Peets E.A, Jackson M and Symchowics. Metabolism of Chlorpheniramine maleate in man J. of Pharmacology and Experimental therapeutic 1972; 180: 464-474.
18. Simons F.E.R., Luciuk H.G. Simons K,J, Pharmacokinetics and efficacy of Chlorpheniramine in children J. Allergy Clin Immunol 1982; 69: 376-381.
19. Watson WTA, Simons KJ, Chen XY, Simons PER. Cetirizine: Pharmacokinetics and pharmacodynamic evaluation in children with seasonal allergic rhinitis J Allergy Clin Immunol 1989; 84: 457-64.
20. Aaronson DW. Comparative efficacy of H<sub>1</sub> antihistamines Annals of Allergy 1991; 67: 541-547.

21. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trial John Wright PSG Inc Boston ; 1983 : 171.
22. Senn S. Cross-over Trials in Clinical research JOHN WILEY & SONS Ltd New York 1993.
23. Rosner B. Fundamentals of biostatistics PWS-KENT Publishing Company Boston : 351-353: 1990.
24. Gengo FM, Gabos C and Mechtler L. Quantitative effects of Cetirizine and diphenhydramine on mental performance measured using an automobile driving stimulator Annals of Allergy 1990: 64: 520-526.
25. Dawson B-Trapp SRG. Basic & Clinical Biostatistics Prentice-Hall International Inc; 1994: 154-157.
26. Fleiss JL. Statistical methods for Rates and proportions JOHN WILEY & SONS New York: 1981: 104-115 .
27. Gehlbach SH. Interpreting the Medical Literature Mac Millan Publishing Company New York: 1988: 61-79 .
28. Drumond M.F. Principles of economic appraisal in health care Oxford University Press 1987: 12-16.
29. Kamolratanakul P., Chunhaswasdikul, Jittinandana A., Tangcharoensathien V., Udomrati N., Akksilp S. Cost-effectiveness of three short-course anti-Tuberculosis programmes compared with a standard regimen in Thailand J Clin Epidemiol 1993: 46: 631-636.

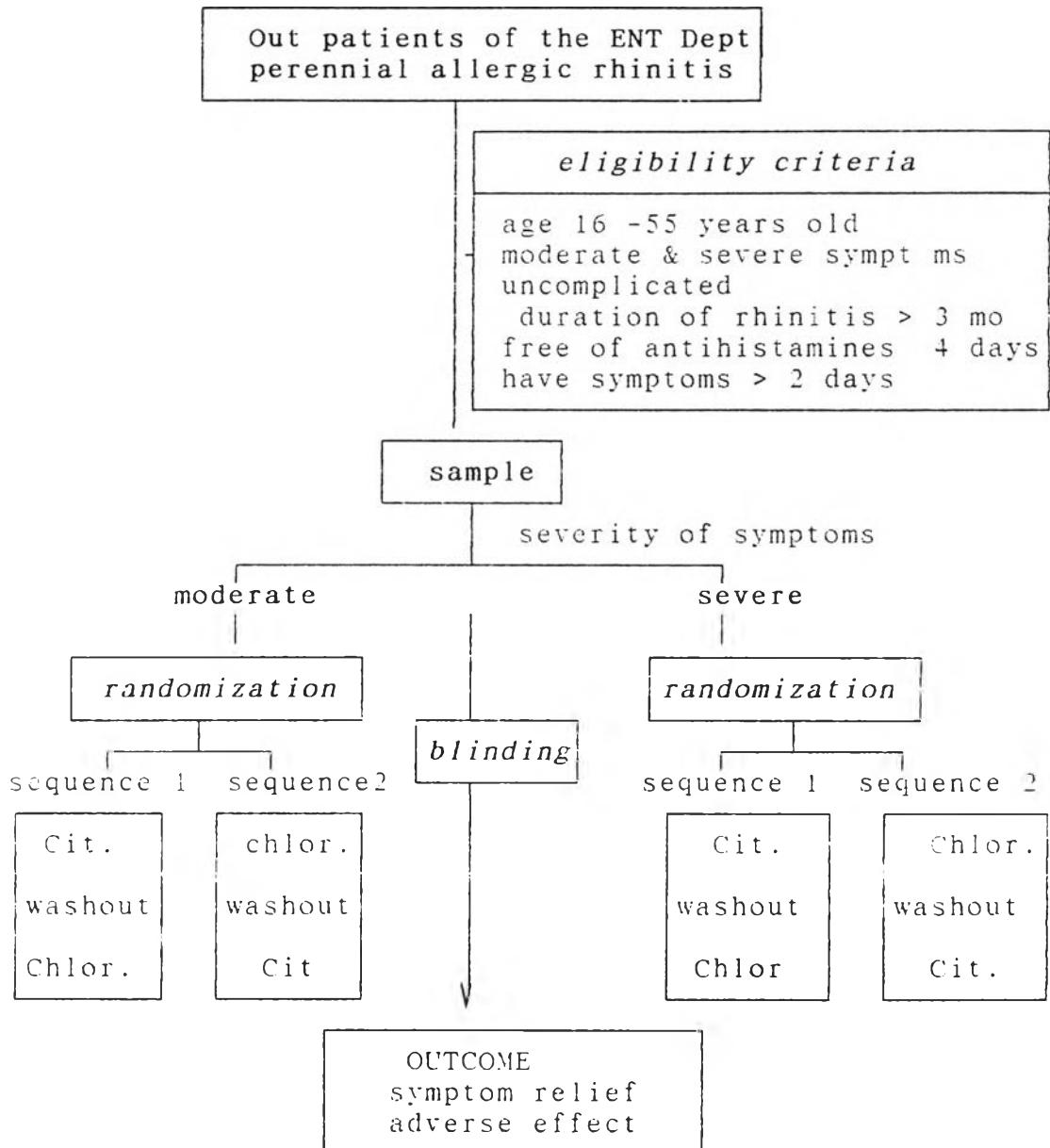
Appendix 1.

PATHOGENESIS OF PERENNIAL ALLERGIC RHINITIS



Appendix 2.

Overview of the study design



### Appendix 3.

#### Calculation of Kappa

##### 6.1. During Cetirizine treatment

		Physician 1		total
		success	failure	
Physician 2	success	58	2	60
	failure	1	11	12
	total	59	13	72

1. Total observed agreement =  $58 + 11 / 72 = 0.95$
2. Positive by chance =  $59 \times 60 / 72 = 49.16$
3. Negative by chance =  $13 \times 12 / 72 = 2.16$
4. proportion of the chance agreement =  $(49.16 + 2.16) / 72 = 0.71$
5. Agreement beyond chance =  $0.95 - 0.71 = 0.24$
6. Potential agreement beyond chance =  $1 - 0.71 = 0.29$
7. Kappa =  $0.24 / 0.29 = 0.82$

##### 6.2. During Chlorpheniramine treatment

		Physician 1.		total
		success	failure	
Physician 2.	success	60	1	61
	failure	1	-	8
	total	61	8	69

1. Total observed agreement =  $60 + 7 / 69 = 0.97$
2. Positive by chance =  $61 \times 61 / 69 = 53.92$
3. Negative by chance =  $8 \times 8 / 69 = 0.92$
4. Proportion for chance agreement  $(53.92 + 0.92) / 69 = 0.79$
5. Agreement beyond chance =  $0.97 - 0.79 = 0.18$
6. Potential agreement beyond chance =  $1 - 0.79 = 0.21$
7. Kappa =  $0.18 / 0.21 = 0.85$

Appendix 4.

The adverse effects event during the treatment:

1. Dry mouth

Excluding dropouts and confounders

		10 mg Cetirizine		
		positive	negative	total
8 mg Chlorpheniramine	pos.	6	12	18
	neg.	8	41	49
	total	14	53	67

$\frac{(|12-8|-1)}{2}$   
 Mc Nemar stat. =  $\frac{|12-8|}{12+8} = 0.45 \rightarrow \text{not significant}$

The 90% confidence interval was  $0.054 < 0.059 < 0.06$

2. Visual disturbance

Excluding dropouts and confounders

		10 mg Cetirizine		
		pos.	neg.	total
8 mg Chlorpheniramine	pos.	3	5	8
	neg.	7	52	59
	total	10	57	67

$\frac{(|5-7|-1)}{2}$   
 Mc Nemar stat. =  $\frac{|5-7|}{5+7} = 0.08 \rightarrow \text{not significant}$   
 90% Confidence interval =  $-0.098 < 0.03 < 0.068$

### 3. Headache

Excluding dropouts and confounders

	10 mg Cetirizine		
	pos.	neg.	total
8 mg Chlorpheniramine pos.	-	15	22
8 mg Chlorpheniramine neg.	8	37	45
	total	15	42
			67

{|15-8|-1}2  
 Mc Nemar stat.= ----- = 1.56 --> not significant  
 $\frac{15 + 8}{15 + 8}$   
 90% Confidence interval = - 0.24 < 0.10 < 0.23

### 4. Urinary problem

Excluding dropouts and confounders

	10 mg Cetirizine		
	pos.	neg.	total
8 mg Chlorpheniramine pos.	0	+	+
8 mg Chlorpheniramine neg.	3	60	63
	total	3	64
			67

{|5-3|-1}2  
 Mc Nemar stat.= ----- = 0.08 -> not significant  
 $\frac{5 + 3}{5 + 3}$   
 90% Confidence interval = - 0.064 < 0.015 < 0.094

Appendix 5.

Day : 1  
Date:

PATIENT RECORD  
(FOR PHYSICIAN)

Code no:....

Name : .....

Address: (complete).....  
.....

---

Baseline data

I. Age : ( ) year

II. Sex : 1. ( ) male  
          2. ( ) female

III. Duration of disease: 1. .... year

          2. .... month

IV. The symptoms occurred about : 1..... PM

2.....AM

---

Please score your rhinitis symptoms using this scale.

0 = no symptoms

1 = symptoms are notice but not disturb activity

2 = symptoms disturb some of activity or sleep

3 = symptoms are disturb activities and sleep

V. Do you have any other allergic symptoms ?

( ) yes

( ) no

( ) Bronchial asthma

( ) urticaria

( ) food allergy

( ) drug allergy

( ) allergic family history

VI. During you have symptoms, which one are very disturbing ?

1. Sneezing

2. Watery secretions

3. Nasal obstruction



( ) ( ) ( )

### Variation of symptoms

- VII. How many times do you sneeze during your worse symptoms ?  
 less than 3 times  
 3 to 5 times  
 6 to 8 times  
 more than 8 / uncountable

- VIII. How many times do you blow out your nasal secretion during that time ?  
 no secretion  
 1 or 2 times  
 repeated blowing  
 profuse nasal secretion

- IX. Do you have nasal obstruction during your worse symptoms ?  
 no obstruction  
 partial obstruction  
 total nasal obstruction

- X. Do you have other symptom during that time ?  
 yes  
 no

The symptoms are :  
 headache  
 smell disturbance  
 taste disturbance  
 fatigue  
 sedation  
 difficult to concentrate

- XI. How long is your worse symptoms happen everyday ?  
 less than half hour  
 30 min. to 1 hour  
 more than 1 hour

### XII. Physical examinations

- The ear :  
 normal  
 abnormal, record:.....

## The Nose :

Nasal mucosa : ( ) pink (normal)  
                   ( ) hyperemia  
                   ( ) pale/ bluish  
 secretion     : ( ) no secretion  
                   ( ) positive  
                   ( ) profuse  
 concha        : ( ) no edema  
                   ( ) partial edema  
                   ( ) severe ( total obstruction)

Paranasal sinuses : ( ) N  
                   ( ) abN

Sinus X Ray : .....

## The throat :

Pharynx :  
 Tonsils :

XIII. Cytologic nasal secretion :  
                   ( ) 1. eosinophil  
                   ( ) 2. neutrophil

XIV. Renal F.T. : Creatinine clearance (      )  
 Liver F.T. : SGPT (      )

## XV. Allergic Skin prick testing

( ) house dust  
  ( ) dust mite  
  ( ) human dander  
  ( ) dog dander  
  ( ) cat dander  
  ( ) milk  
  ( ) egg

RHINITIS SYMPTOMS DIARY CARD  
(for patient)

Name : .....

Date :

Code no : .....

Period (I) (II)

Address : .....

Please score your rhinitis symptoms using this scale and record in the following place at 8.00 p.m. and at 7.00 a.m.

0 = no symptoms

1 = symptoms are notice but not disturb activity

2 = symptoms disturb some of activity or sleep

3 = symptoms are disturb patient's activities and sleep

## RHINITIS SYMPTOM SCORE

## D A Y

1	2	3	4	5	6	7
N. M.						
( ) ( )	( ) ( )	( ) ( )	( ) ( )	( ) ( )	( ) ( )	( ) ( )

## ADVERSE EFFECT RECORD

Please record if you experience unusual sensation during the treatment.

	D a y						
	1	2	3	4	5	6	7
I. Do you feel something discomfort during taking the drug?	( )	( )	( )	( )	( )	( )	( )
1. Yes							
2. No.							
II. What feeling did you experience?	( )	( )	( )	( )	( )	( )	( )
1. Dry mouth	( )	( )	( )	( )	( )	( )	( )
2. Blurred vision	( )	( )	( )	( )	( )	( )	( )
3. Urinary discomfort	( )	( )	( )	( )	( )	( )	( )
4. Headache	( )	( )	( )	( )	( )	( )	( )
5. Somnolence / drowsiness	( )	( )	( )	( )	( )	( )	( )
III. If you have somnolence feeling please score with following scale:	( )	( )	( )	( )	( )	( )	( )
1. feeling active, wide awake	( )	( )	( )	( )	( )	( )	( )
2. functioning at not peak, able to concentrate	( )	( )	( )	( )	( )	( )	( )
3. relaxed awake but not fully alert	( )	( )	( )	( )	( )	( )	( )
4. a little foggy, let down	( )	( )	( )	( )	( )	( )	( )
5. beginning to lose track, difficulty in staying awake	( )	( )	( )	( )	( )	( )	( )
6. sleepy, prefer to lie down	( )	( )	( )	( )	( )	( )	( )
7. cannot stay awake	( )	( )	( )	( )	( )	( )	( )

## Appendix 6.

Patient's symptom scores during treatment.  
Symptom score

continous

## symptom score

sequence	patient number	Cetirizine						Chlorpheniramine					
		DAY						DAY					
		1	2	3	4	5	6	1	2	3	4	5	6
CTM/ Cet	1	1	1	1	1	1	1	2	2	2	2	2	2
	2	1	2	1	1	1	2	1	2	2	1	2	1
	6	2	2	2	2	2	2	2	2	2	2	2	0
	8	1	1	1	1	1	1	1	0	1	0	0	0
s	10	0	0	1	0	0	0	0	2	2	2	2	3
e	34	3	3	2	0	0	0	0	2	3	3	2	3
v	35	1	1	1	1	1	1	2	1	1	1	1	0
r	37	1	0	1	1	1	1	1	0	1	1	1	1
e	39	1	1	1	1	1	2	1	1	1	1	1	1
e	40	1	1	1	1	1	0	1	1	1	1	0	0
	51	1	1	0	2	2	2	2	2	2	2	2	2
	52	2	1	2	2	1	1	1	2	1	2	1	1
	53	1	1	1	1	1	1	1	1	1	1	1	1
	56	1	0	0	0	1	1	1	0	0	0	0	0
	58	2	2	2	2	2	2	2	2	2	2	1	1
	71	2	3	3	2	2	2	2	0	0	0	0	0
	73	1	1	1	1	1	1	2	2	1	1	1	1
	76	1	1	3	1	1	1	1	0	1	1	1	1
	77	1	1	2	2	2	2	1	1	1	1	1	1
SO.	no case												
	12 *	0	0	0	0	0	0	0	0	0	0	0	0
m	13	1	0	0	0	3	1	0	1	1	1	1	1
o	16	0	0	0	0	0	1	0	1	1	1	1	1
d	19	0	0	0	0	0	0	0	0	1	1	1	0
e	20	0	0	0	0	0	0	0	0	0	0	0	0
r	21	0	0	0	0	0	0	0	1	0	0	0	0
a	22	2	1	1	2	1	0	0	1	1	1	1	1
a	27	0	0	0	0	0	0	0	0	2	2	1	0
t	28	0	0	0	0	0	0	0	1	1	1	0	0
e	30	2	0	0	0	0	0	0	2	2	2	3	3
	42	1	0	2	0	1	1	1	1	2	2	2	1
	43	1	1	0	0	0	1	0	0	0	0	0	0
	45	1	0	0	0	0	0	0	1	1	0	0	0
	48	0	1	0	0	0	1	1	2	2	2	2	2
	50	1	1	1	1	0	0	0	1	2	1	2	1
	61	0	1	0	1	1	1	1	1	0	0	0	0
	62	0	0	0	0	0	0	0	1	1	2	2	1
	65	0	0	0	0	0	0	0	0	0	0	0	0
	68	1	0	0	0	0	0	0	2	1	1	1	1
	69	0	0	0	0	0	0	0	1	0	0	0	0

## Appendix 7. Patient's sedation side effect score Sedation score

continued

## sedation score

sequence number	patient number	Cetirizine							Chlorpheniramine						
		1	2	3	4	5	6	7	1	2	3	4	5	6	7
CTM/ Cet	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	6	6	1	1	-	5
	6	-	-	-	6	6	6	6	-	-	6	6	6	6	6
	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
s	10	-	-	-	-	-	-	-	-	1	1	2	3	3	3
e	34	-	-	-	-	-	-	-	-	-	-	6	6	6	6
v	35	-	-	-	-	-	-	-	-	6	6	2	4	4	4
e	37	-	-	-	-	-	-	-	-	-	-	-	-	-	-
r	39	1	-	3	4	6	7	7	-	-	-	-	-	-	-
e	40	-	-	-	-	-	-	-	-	3	3	2	3	3	3
51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52	-	-	-	-	-	-	-	-	-	5	5	2	3	3	3
53	-	-	-	-	-	-	-	-	-	5	5	3	3	3	3
56	-	-	-	-	-	-	-	-	-	5	5	3	3	3	3
58	6	-	3	3	3	3	3	3	-	6	6	6	6	6	6
71	-	-	-	-	-	-	-	-	-	3	3	3	3	3	3
73	-	-	-	-	-	-	-	-	-	2	2	2	2	2	2
76	-	-	-	-	-	-	-	-	-	1	3	-	-	-	-
77	-	-	-	-	-	-	-	-	-	6	4	-	-	-	-
80.	no case	-	-	-	-	-	-	-	-	2	2	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
m	16	-	-	-	-	-	-	-	-	6	-	-	6	6	-
o	19	-	-	-	-	-	-	-	-	4	3	3	1	2	3
d	20	-	6	6	6	6	6	4	-	6	6	6	6	6	6
e	21	-	-	-	-	-	-	-	-	2	-	-	-	-	-
r	22	-	-	-	-	-	-	-	-	-	-	-	-	-	-
a	27	-	-	-	-	-	-	-	-	-	-	-	-	-	-
t	28	-	-	-	-	-	-	-	-	3	3	3	3	2	3
e	30	-	-	-	-	-	-	-	-	6	6	6	6	6	6
42	3	3	3	3	3	-	-	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-	-	-	3	3	3	3	3
45	3	3	3	3	3	3	3	3	-	3	3	3	3	3	3
48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50	3	3	3	3	3	3	3	3	-	3	3	3	3	3	3
61	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-
65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-
69	4	4	4	4	4	4	4	4	-	-	-	-	-	-	-

## Appendix 8.

## Data of the physician assessment,

Cetirizine/Chlorpheniramine  
Periode I                    Periode II

## Number

3	S	S
4	S	S
5	S	S
6	S	S
7	-	-
8	D., O.	-
31	E	S
32	S	S
33	S	S
36	S	S
38	S	F
54	S	D., O.
55	S	S
57	S	S
59	S	S
60	S	D., O.
72	S	S
74	S	S
75	F	S
78	S	F
79	S	S
47*	F	S
48	F	S
23	D., O.	-
24	S	E
25	S	S
26	S	S
29	S	S
41	F	E
44	S	S
46	S	D., O.
47	F	S
49	F	S
63	S	S
64	S	S
66	D., O.	-
67	S	S
70	D., O.	-

note: 2 to 79 : severe cases

17 to 70 : moderate cases

Continued : Chlorpheniramine/ Cetirizine  
Periode I Periode II

VITAE

Mrs Suprihati Asmuni was born on June 21, 1950 in Banjarnegara, Indonesia. She graduated as General Physician from Faculty of Medicine, Diponegoro University, Semarang in 1976 and further study in Otolaryngology and got the Diploma in 1983.

She has been enrolled in the Master's degree in Health Development at Faculty of Medicine, Chulalongkorn University Bangkok under The THAI CERTC Consortium since June 1994. She is now in charge of the Rhinology Subdivision, department of Otolaryngology, Faculty of Medicine Diponegoro University in Semarang, Indonesia.

