Clozaril® (clozapine) Tablets

Briefing Document for Psychopharmacological Drugs Advisory
Committee Meeting (June 16, 2003)

Appendix 1: Post-text tables (United States Data)

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1 Post-text tables

United States Data

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Post-text table 3.1-1
Summary of demographic information by cohort
All patients
(Excluding patient's data met criteria 1, 2, and 3) [1]

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| | | -- Cohort -- | | | | |
		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [2]
Age	<=35	37453 (38.4%)	12671 (30.6%)	12794 (32.6%)	50124 (36.1%)	<0.0001
	36-50	37812 (38.8%)	15413 (37.3%)	14808 (37.7%)	53225 (38.3%)	
	51-65	11517 (11.8%)	5957 (14.4%)	6073 (15.5%)	17474 (12.6%)	
	>65	8015 (8.2%)	6848 (16.6%)	4761 (12.1%)	14863 (10.7%)	
	Missing	2688 (2.8%)	470 (1.1%)	824 (2.1%)	3158 (2.3%)	
	Total	97485 (100.0%)	41359 (100.0%)	39260 (100.0%)	138844 (100.0%)	
	Mean	40.8	45.0	43.0	42.1	
	STD	14.2	17.3	16.7	15.3	
Gender N (%)	Male	56156 (57.6%)	23100 (55.9%)	22287 (56.8%)	79256 (57.1%)	0.1342
	Female	38641 (39.6%)	17789 (43.0%)	16149 (41.1%)	56430 (40.6%)	
	Missing	2688 (2.8%)	470 (1.1%)	824 (2.1%)	3158 (2.3%)	

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[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[2] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3

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                                        Post-text table 3.1-1 (Continued)
                                    Summary of demographic information by cohort
                                                   All patients
                              (Excluding patient's data met criteria 1, 2, and 3) [1]
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                      --------------------------------------- Cohort ---------------------------------------
                      Cohort 1            Cohort 2            Cohort 3            Cohorts 1 and 2     p-value [2]
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Race N (%)	White	67380 (69.1%)	28578 (69.1%)	24528 (62.5%)	95958 (69.1%)	<0.0001
	Black	11533 (11.8%)	5834 (14.1%)	6058 (15.4%)	17367 (12.5%)	
	Hispanic	3914 (4.0%)	1905 (4.6%)	2014 (5.1%)	5819 (4.2%)	
	Oriental	1246 (1.3%)	479 (1.2%)	460 (1.2%)	1725 (1.2%)	
	Other	1012 (1.0%)	566 (1.4%)	724 (1.8%)	1578 (1.1%)	
	Missing	12400 (12.7%)	3997 (9.7%)	5476 (13.9%)	16397 (11.8%)	

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[1] Criteria 1: Excluded patients with only one record of WBC;
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                                Post-text table 3.1-2
                        Summary of demographic information by cohort
                           Patients with moderate leukopenia [1]
                     With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
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		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [3]
Age	<=35	1288 (35.1%)	191 (23.6%)	176 (28.9%)	1479 (33.0%)	0.0002
	36-50	1459 (39.7%)	267 (32.9%)	206 (33.9%)	1726 (38.5%)	
	51-65	546 (14.9%)	160 (19.7%)	116 (19.1%)	706 (15.7%)	
	>65	365 (9.9%)	184 (22.7%)	104 (17.1%)	549 (12.2%)	
	Missing	15 (0.4%)	9 (1.1%)	6 (1.0%)	24 (0.5%)	
	Total	3673 (100.0%)	811 (100.0%)	608 (100.0%)	4484 (100.0%)	
	Mean	42.2	49.3	46.0	43.5	
	STD	14.8	17.6	18.0	15.6	
Gender N (%)	Male	1968 (53.6%)	409 (50.4%)	319 (52.5%)	2377 (53.0%)	0.8877
	Female	1690 (46.0%)	393 (48.5%)	283 (46.5%)	2083 (46.5%)	
	Missing	15 (0.4%)	9 (1.1%)	6 (1.0%)	24 (0.5%)	

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[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[3] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3
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                                   Post-text table 3.1-2 (Continued)
                                Summary of demographic information by cohort
                                   Patients with moderate leukopenia [1]
                          With data cut-off date of 01-Apr-1998 for cohorts 1 and 2


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                 ---------------------------------------- Cohort ----------------------------------------
                 Cohort 1            Cohort 2            Cohort 3            Cohorts 1 and 2    p-value [3]
_____

Race N (%)      White        2559 ( 69.7%)      560 ( 69.1%)      376 ( 61.8%)      3119 ( 69.6%)    <0.0001
                Black         382 ( 10.4%)      111 ( 13.7%)      107 ( 17.6%)       493 ( 11.0%)
                Hispanic      133 (  3.6%)       41 (  5.1%)       30 (  4.9%)       174 (  3.9%)
                Oriental       49 (  1.3%)        5 (  0.6%)        5 (  0.8%)        54 (  1.2%)
                Other          42 (  1.1%)        7 (  0.9%)        9 (  1.5%)        49 (  1.1%)
                Missing       508 ( 13.8%)       87 ( 10.7%)       81 ( 13.3%)       595 ( 13.3%)

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[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
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[3] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3




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Post-text table 3.1-3
Summary of demographic information by cohort
Patients with severe leukopenia [1]
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2

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		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [3]
Age	<=35	74 (16.2%)	21 (22.3%)	9 (15.8%)	95 (17.2%)	0.9643
	36-50	204 (44.5%)	28 (29.8%)	23 (40.4%)	232 (42.0%)	
	51-65	117 (25.5%)	31 (33.0%)	16 (28.1%)	148 (26.8%)	
	>65	62 (13.5%)	14 (14.9%)	9 (15.8%)	76 (13.8%)	
	Missing	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
	Total	458 (100.0%)	94 (100.0%)	57 (100.0%)	552 (100.0%)	
	Mean	48.1	48.3	50.0	48.1	
	STD	13.8	14.7	16.0	14.0	
Gender N (%)	Male	241 (52.6%)	55 (58.5%)	30 (52.6%)	296 (53.6%)	0.8753
	Female	216 (47.2%)	39 (41.5%)	27 (47.4%)	255 (46.2%)	
	Missing	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	

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[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
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[3] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3

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                                   Post-text table 3.1-3 (Continued)
                                 Summary of demographic information by cohort
                                     Patients with severe leukopenia [1]
                          With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
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                   -------------------------------------- Cohort --------------------------------------
                   Cohort 1            Cohort 2            Cohort 3            Cohorts 1 and 2    p-value [3]
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Race N (%)    White        309 ( 67.5%)        79 ( 84.0%)        40 ( 70.2%)        388 ( 70.3%)     0.2158
              Black          9 (  2.0%)         3 (  3.2%)         4 (  7.0%)         12 (  2.2%)
              Hispanic      19 (  4.1%)         5 (  5.3%)         4 (  7.0%)         24 (  4.3%)
              Oriental       2 (  0.4%)         0 (  0.0%)         0 (  0.0%)          2 (  0.4%)
              Other          6 (  1.3%)         1 (  1.1%)         0 (  0.0%)          7 (  1.3%)
              Missing      113 ( 24.7%)         6 (  6.4%)         9 ( 15.8%)        119 ( 21.6%)

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[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
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                                     Post-text table 3.1-4
                            Summary of demographic information by cohort
                                    Patients with agranulocytosis
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
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		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [2]
Age	<=35	93 (21.5%)	16 (18.8%)	13 (23.2%)	109 (21.1%)	0.6035
	36-50	174 (40.3%)	26 (30.6%)	18 (32.1%)	200 (38.7%)	
	51-65	124 (28.7%)	35 (41.2%)	17 (30.4%)	159 (30.8%)	
	>65	41 (9.5%)	8 (9.4%)	8 (14.3%)	49 (9.5%)	
	Total	432 (100.0%)	85 (100.0%)	56 (100.0%)	517 (100.0%)	
	Mean	46.5	48.2	47.7	46.8	
	STD	13.4	13.1	15.4	13.4	
Gender N (%)	Male	232 (53.7%)	51 (60.0%)	31 (55.4%)	283 (54.7%)	0.9296
	Female	200 (46.3%)	34 (40.0%)	25 (44.6%)	234 (45.3%)	

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[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[2] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3
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Post-text table 3.1-4 (Continued)
Summary of demographic information by cohort
Patients with agranulocytosis
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2

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| | | ----- Cohort ----- | | | | |
		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [2]
Race N (%)	White	277 (64.1%)	72 (84.7%)	37 (66.1%)	349 (67.5%)	0.6171
	Black	13 (3.0%)	2 (2.4%)	3 (5.4%)	15 (2.9%)	
	Hispanic	22 (5.1%)	2 (2.4%)	4 (7.1%)	24 (4.6%)	
	Oriental	3 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	
	Other	6 (1.4%)	1 (1.2%)	0 (0.0%)	7 (1.4%)	
	Missing	111 (25.7%)	8 (9.4%)	12 (21.4%)	119 (23.0%)	

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[1] Criteria 1: Excluded patients with only one record of WBC;
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    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[2] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3

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                                          Post-text table 3.1-5
                                 Summary of demographic information by cohort
                                        Patients who discontinued [1]
                            With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
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		Cohort				
		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [3]
Age	<=35	27291 (41.4%)	7483 (32.7%)	7440 (34.0%)	34774 (39.2%)	<0.0001
	36-50	25990 (39.4%)	8349 (36.5%)	8259 (37.7%)	34339 (38.7%)	
	51-65	7111 (10.8%)	3169 (13.9%)	3281 (15.0%)	10280 (11.6%)	
	>65	4699 (7.1%)	3729 (16.3%)	2644 (12.1%)	8428 (9.5%)	
	Missing	823 (1.2%)	122 (0.5%)	269 (1.2%)	945 (1.1%)	
	Total	65914 (100.0%)	22852 (100.0%)	21893 (100.0%)	88766 (100.0%)	
	Mean	39.8	44.4	42.6	41.0	
	STD	13.6	17.4	16.7	14.8	
Gender N (%)	Male	38876 (59.0%)	12743 (55.8%)	12518 (57.2%)	51619 (58.2%)	0.0175
	Female	26215 (39.8%)	9987 (43.7%)	9106 (41.6%)	36202 (40.8%)	
	Missing	823 (1.2%)	122 (0.5%)	269 (1.2%)	945 (1.1%)	

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[1] Discontinuation is defined as follows:
    If a patient had a gap between WBC counts greater than 15 days during weekly monitoring or a gap between WBC counts
    greater than 30 days during bi-weekly monitoring then start date of the gap is defined as the date of discontinuation.
    For patients who discontinued on multiple occurrences then only the first point of discontinuation is utilized.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[3] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3
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Post-text table 3.1-5 (Continued)
Summary of demographic information by cohort
Patients who discontinued [1]
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2

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| | | --------------------------------------- Cohort --------------------------------------- | | | | |
		Cohort 1	Cohort 2	Cohort 3	Cohorts 1 and 2	p-value [3]
Race N (%)	White	48081 (72.9%)	15869 (69.4%)	13847 (63.2%)	63950 (72.0%)	<0.0001
	Black	8150 (12.4%)	3290 (14.4%)	3402 (15.5%)	11440 (12.9%)	
	Hispanic	2913 (4.4%)	1190 (5.2%)	1261 (5.8%)	4103 (4.6%)	
	Oriental	958 (1.5%)	285 (1.2%)	273 (1.2%)	1243 (1.4%)	
	Other	726 (1.1%)	335 (1.5%)	379 (1.7%)	1061 (1.2%)	
	Missing	5086 (7.7%)	1883 (8.2%)	2731 (12.5%)	6969 (7.9%)	

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[1] Discontinuation is defined as follows:
    If a patient had a gap between WBC counts greater than 15 days during weekly monitoring or a gap between WBC counts
    greater than 30 days during bi-weekly monitoring then start date of the gap is defined as the date of discontinuation.
    For patients who discontinued on multiple occurrences then only the first point of discontinuation is utilized.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
[3] From Pearson Chi-square test (excluding missing values) to compare Cohorts 1 and 2 with Cohort 3

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Post-text table 3.1-6a
Summary of demographic information in cohort 3
Patients who switched to bi-weekly monitoring after 6 months treatment
(Excluding patient's data meeting criteria 1, 2, and 3) [1]

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                                                                          Cohort 3
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Age   <=35   6294 (35.1%)
                36-50   7160 (39.9%)
                51-65   2590 (14.4%)
                >65   1797 (10.0%)
                Missing   115 (0.6%)
                Total   17956 (100.0%)
                Mean   41.7
                STD   15.8

Gender N (%)   Male   10530 (58.6%)
                Female   7311 (40.7%)
                Missing   115 (0.6%)

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[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.

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                                  Post-text table 3.1-6a (Continued)
                              Summary of demographic information for cohort 3
                       Patients who switched to bi-weekly monitoring after 6 months treatment
                           (Excluding patient's data meeting criteria 1, 2, and 3) [1]


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                                                                                   Cohort 3
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Race N (%)      White                                                           11626 ( 64.7%)
                Black                                                            2679 ( 14.9%)
                Hispanic                                                          983 (  5.5%)
                Oriental                                                          228 (  1.3%)
                Other                                                             306 (  1.7%)
                Missing                                                          2134 ( 11.9%)


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[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
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                                    Post-text table 3.1-6b
                        Summary of demographic information in cohort 3
                          Patients on weekly monitor after 6 months treatment
                        (Excluding patient's data met criteria 1, 2, and 3) [1]


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                                                                          Cohort 3
_____

Age             <=35                                                  1392 ( 32.7%)
                36-50                                                 1628 ( 38.3%)
                51-65                                                  665 ( 15.6%)
                >65                                                    519 ( 12.2%)
                Missing                                                 49 (  1.2%)
                Total                                                 4253 (100.0%)
                Mean                                                            43.0
                STD                                                             16.8

Gender N (%)    Male                                                  2493 ( 58.6%)
                Female                                                1711 ( 40.2%)
                Missing                                                 49 (  1.2%)

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[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.




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                                  Post-text table 3.1-6b (Continued)
                               Summary of demographic information in cohort 3
                              Patients on weekly monitor after 6 months treatment
                            (Excluding patient's data met criteria 1, 2, and 3) [1]


_____

                                                                                 Cohort 3
_____

Race N (%)      White                                                         2567 ( 60.4%)
                Black                                                          760 ( 17.9%)
                Hispanic                                                       196 (  4.6%)
                Oriental                                                        35 (  0.8%)
                Other                                                           78 (  1.8%)
                Missing                                                        617 ( 14.5%)


_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.




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Novartis Pharmaceuticals Corporation                                                  Page 1 of 2
Clozaril (clozapine)
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                                   Post-text table 3.2-1a
                        Summary statistics for incidence of agranulocytosis
                                        All duration
                     With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                       (Excluding patient's data met criteria 1, 2, and 3) [1]


_____


Cohort                                 Category                               All Duration
_____


Cohort 1                               Incidence/1000 patient year                   1.350
                                       Number of incidence                             432
                                       Number of patient                             97485
                                       Total patient year                           319972

Cohort 2                               Incidence/1000 patient year                   1.778
                                       Number of incidence                              85
                                       Number of patient                             41359
                                       Total patient year                            47818

Cohort 3                               Incidence/1000 patient year                   1.360
                                       Number of incidence                              56
                                       Number of patient                             39260
                                       Total patient year                            41172


_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.




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Clozaril (clozapine)

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Post-text table 3.2-1a (Continued)
Summary statistics for incidence of agranulocytosis
All duration
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
(Excluding patient's data met criteria 1, 2, and 3) [1]

_____

Cohort	Category	All Duration
Cohorts 1 and 2	Incidence/1000 patient year	1.406
	Number of incidence	517
	Number of patient	138844
	Total patient year	367790
Cohorts 1, 2, and 3	Incidence/1000 patient year	1.401
	Number of incidence	573
	Number of patient	178104
	Total patient year	408962

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                                          Post-text table 3.2-1b
                              Summary statistics for incidence of agranulocytosis
                                    By duration of 1 - 6 months and > 6 months
                             With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                              (Excluding patient's data met criteria 1, 2, and 3) [1]


_____

                                                              ------------- Duration -------------
Cohort                                Category                (1 - 6] Months          > 6 Months
_____


Cohort 1                              Incidence/1000 patient year          7.563                0.420
                                      Number of incidence                   315                  117
                                      Number of patient                   97485                75635
                                      Total patient year                  41649               278324

Cohort 2                              Incidence/1000 patient year          4.724                0.224
                                      Number of incidence                    78                    7
                                      Number of patient                   41359                28673
                                      Total patient year                  16513                31305

Cohort 3                              Incidence/1000 patient year          3.250                0.370
                                      Number of incidence                    46                   10
                                      Number of patient                   39260                22209
                                      Total patient year                  14152                27020

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.



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<div align="center">
Post-text table 3.2-1b (Continued)
Summary statistics for incidence of agranulocytosis
By duration of 1 - 6 months and > 6 months
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
(Excluding patient's data met criteria 1, 2, and 3) [1]
</div>

_____

Cohort	Category	Duration (1 - 6] Months	> 6 Months
Cohorts 1 and 2	Incidence/1000 patient year	6.757	0.400
	Number of incidence	393	124
	Number of patient	138844	104308
	Total patient year	58162	309628
Cohorts 1, 2, and 3	Incidence/1000 patient year	6.071	0.398
	Number of incidence	439	134
	Number of patient	178104	126517
	Total patient year	72314	336648

_____

```
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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                                    Post-text table 3.2-1c
                        Summary statistics for incidence of agranulocytosis
                        By duration of treatment (1 - 18, 19 - 52, and > 52 weeks)
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                        (Excluding patient's data meeting criteria 1, 2, and 3) [1]

_____

                                              ------------------------ Duration ------------------------
Cohort                      Category          (0-18] Weeks       (18-52] Weeks          >52 Weeks
_____

Cohort 1                    Incidence/1000 patient year       9.833              0.882               0.400
                            Number of incidence                293                 42                  97
                            Number of patient                97485              79038               68534
                            Total patient year               29797              47599              242576


Cohort 2                    Incidence/1000 patient year       6.099              0.479               0.209
                            Number of incidence                 73                  8                   4
                            Number of patient                41359              30675               20846
                            Total patient year               11969              16717               19132

Cohort 3                    Incidence/1000 patient year       3.797              1.077               0.113
                            Number of incidence                 40                 14                   2
                            Number of patient                39260              25093               15936
                            Total patient year               10535              12997               17640

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.



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                               Post-text table 3.2-1c (Continued)
                        Summary statistics for incidence of agranulocytosis
                      By duration of treatment (1 - 18, 19 - 52, and > 52 weeks)
                      With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                       (Excluding patient's data meeting criteria 1, 2, and 3) [1]


_____

                                         ------------------------ Duration ------------------------
Cohort                     Category        (0-18] Weeks        (18-52] Weeks          >52 Weeks
_____

Cohorts 1 and 2            Incidence/1000 patient year        8.763               0.777              0.386
                           Number of incidence                 366                  50                101
                           Number of patient                 138844              109713              89380
                           Total patient year                 41766               64315             261708

Cohorts 1, 2, and 3        Incidence/1000 patient year        7.763               0.828              0.369
                           Number of incidence                 406                  64                103
                           Number of patient                 178104              134806             105316
                           Total patient year                 52301               77312             279348

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.




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                                         Post-text table 3.2-1d
                    Number of patients with WBC <= 1000 at the time of agranulocytosis [1]
                            With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                             (Excluding patient's data met criteria 1, 2, and 3) [2]


_____

                                -------------------------------- Cohort --------------------------------
                                Cohort 1             Cohort 2             Cohort 3             Cohorts 1 and 2
_____

WBC <= 1000/mm^3        Yes     122 ( 28.2%)         24 ( 28.2%)          11 ( 19.6%)          146 ( 28.2%)
                        No      310 ( 71.8%)         61 ( 71.8%)          45 ( 80.4%)          371 ( 71.8%)
                        Total   432 (100.0%)         85 (100.0%)          56 (100.0%)          517 (100.0%)

_____
[1] Within 30 days before or 5 days after date of agranulocytosis, as reported in CNR
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.




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Post-text table 3.2-2: Life table for incidence of agranulocytosis for Cohorts 1 & 2
with data cut-off date of 1-Apr-1998
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	393	393	138844	0.0000	0.0000	0.0000	6.4651	5.8259	7.1043
0.5-1	23	416	104308	3.2273	2.9088	3.5459	0.4750	0.2809	0.6691
1-2	33	449	89380	3.4640	3.1312	3.7969	0.4140	0.2728	0.5553
2-3	25	474	70022	3.8766	3.5153	4.2378	0.4012	0.2439	0.5585
3-4	15	489	54597	4.2761	3.8825	4.6697	0.3102	0.1532	0.4672
4-5	11	500	42117	4.5850	4.1616	5.0083	0.3113	0.1273	0.4952
5-6	14	514	28565	4.8947	4.4336	5.3559	0.6266	0.2984	0.9548
6-7	2	516	16120	5.5181	4.9534	6.0828	0.1731	0.0000	0.4131
7-8	1	517	6983	5.6903	5.0773	6.3032	0.2328	0.0000	0.6892
8-9	0	517	1607	5.9217	5.1593	6.6842	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.2-3: Life table for incidence of agranulocytosis for Cohort 3

(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	46	46	39260	0.0000	0.0000	0.0000	2.9934	2.1284	3.8584
0.5-1	8	54	22209	1.4956	1.0637	1.9274	0.8389	0.2576	1.4202
1-2	2	56	15936	1.9143	1.3942	2.4344	0.1678	0.0000	0.4003
2-3	0	56	7903	2.0818	1.5123	2.6512	0.0000	-	-
3-4	0	56	2638	2.0818	1.5123	2.6512	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.2-4: Life table for incidence of agranulocytosis for all 3 Cohorts
with data cut-off date of 1-Apr-1998 for Cohorts 1 & 2
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	439	439	178104	0.0000	0.0000	0.0000	5.7645	5.2253	6.3038
0.5-1	31	470	126517	2.8781	2.6093	3.1470	0.5349	0.3466	0.7232
1-2	35	505	105316	3.1448	2.8601	3.4294	0.3820	0.2555	0.5086
2-3	25	530	77925	3.5255	3.2142	3.8368	0.3699	0.2249	0.5149
3-4	15	545	57235	3.8940	3.5510	4.2371	0.3020	0.1491	0.4548
4-5	11	556	42117	4.1948	3.8196	4.5700	0.3113	0.1273	0.4952
5-6	14	570	28565	4.5047	4.0873	4.9221	0.6266	0.2984	0.9548
6-7	2	572	16120	5.1283	4.5985	5.6580	0.1731	0.0000	0.4131
7-8	1	573	6983	5.3005	4.7196	5.8814	0.2328	0.0000	0.6892
8-9	0	573	1607	5.5321	4.7950	6.2691	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.2-5
Summary statistics for incidence of agranulocytosis
By calendar year
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
(Excluding patient's data met criteria 1, 2, and 3) [1]

Cohort: Cohorts 1 and 2

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of new patients started Clozaril	9639.0	13763.0	22024.0	25444.0	19750.0	19603.0	19195.0	9426.0	0.0
% of new patients [3]	100.0	61.7	53.8	41.7	27.3	24.9	22.1	11.5	0.0
Number of patients taking drug during the year	9639.0	22293.0	40931.0	61004.0	72336.0	78749.0	86812.0	81877.0	68131.0
Patient year	4463.0	13078.8	27365.2	44148.1	55726.7	63485.8	72111.1	70886.6	16524.7
Number of agranulocytosis	42.0	68.0	91.0	88.0	55.0	67.0	78.0	23.0	5.0
Rate of agranulocytosis / 1000 patients	4.4	3.1	2.2	1.4	0.8	0.9	0.9	0.3	0.1
Incidence / 1000 patient year	9.4	5.2	3.3	2.0	1.0	1.1	1.1	0.3	0.3

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
         will be excluded after the first generic clozapine.

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                        Post-text table 3.2-5 (Continued)
                  Summary statistics for incidence of agranulocytosis
                                  By calendar year
                With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                  (Excluding patient's data met criteria 1, 2, and 3) [1]
```

Cohort: Cohort 3

_____

Category	1997	1998	1999	2000	2001
Number of new patients started Clozaril	3206.0	12602.0	11786.0	8186.0	3480.0
% of new patients [3]	100.0	82.3	53.2	36.8	21.0
Number of patients taking drug during the year	3206.0	15313.0	22156.0	22265.0	16573.0
Patient year	386.7	6853.1	13053.3	13967.2	6911.6
Number of agranulocytosis	1.0	20.0	14.0	17.0	4.0
Rate of agranulocytosis / 1000 patients	0.3	1.3	0.6	0.8	0.2
Incidence / 1000 patient year	2.6	2.9	1.1	1.2	0.6

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
               will be excluded after the first generic clozapine.

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Post-text table 3.2-6
Summary statistics for incidence of agranulocytosis
After 6 months treatment
By calendar year
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2

Cohort: Cohorts 1 and 2

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of patients taking drug during the year	4273.0	12842.0	27239.0	44500.0	58026.0	65234.0	74632.0	75798.0	67986.0
Patient year	1074.2	7662.5	18182.5	33514.5	47178.0	55554.0	63953.6	66276.6	16232.3
Number of agranulocytosis	2.0	4.0	12.0	16.0	18.0	23.0	35.0	10.0	4.0
Rate of agranulocytosis / 1000 patients	0.5	0.3	0.4	0.4	0.3	0.4	0.5	0.1	0.1
Incidence / 1000 patient year	1.9	0.5	0.7	0.5	0.4	0.4	0.5	0.2	0.2

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
              will be excluded after the first generic clozapine.

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                    Post-text table 3.2-6 (Continued)
              Summary statistics for incidence of agranulocytosis
                         After 6 months treatment
                            By calendar year
           With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
```

Cohort: Cohort 3

_____

Category	1998	1999	2000	2001
Number of patients taking drug during the year	6329.0	13766.0	15830.0	12750.0
Patient year	2201.7	8322.2	10838.0	5658.1
Number of agranulocytosis	1.0	3.0	2.0	4.0
Rate of agranulocytosis / 1000 patients	0.2	0.2	0.1	0.3
Incidence / 1000 patient year	0.5	0.4	0.2	0.7

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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Post-text table 3.2-7: Yearly conditional risk per 1000 patients for Cohorts 1 & 2
with data cut-off date of 1-Apr-1998
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	Agranulocytosis					Severe Leukopenia				
	# of occur.	Cond. risk	Std. Error	Lower 95% C.L.	Upper 95% C.L.	# of occur.	Cond. risk	Std. Error	Lower 95% C.L.	Upper 95% C.L.
Yr. 0-1	416	3.639	0.178	3.290	3.988	435	3.805	0.182	3.448	4.162
0.5-1.5	41	0.446	0.070	0.309	0.582	54	0.587	0.080	0.431	0.744
1-2	33	0.414	0.072	0.273	0.555	36	0.452	0.075	0.304	0.599
2-3	25	0.401	0.080	0.244	0.558	26	0.417	0.082	0.257	0.578
3-4	15	0.310	0.080	0.153	0.467	20	0.414	0.092	0.232	0.595
4-5	11	0.311	0.094	0.127	0.495	15	0.424	0.110	0.210	0.639
5-6	14	0.626	0.167	0.298	0.954	11	0.492	0.148	0.201	0.783
6-7	2	0.173	0.122	0.000	0.413	5	0.433	0.194	0.054	0.813
7-8	1	0.233	0.233	0.000	0.689	4	0.932	0.466	0.019	1.844
8-9	0	0.000	0.000	0.000	0.000	0	0.000	0.000	0.000	0.000

Post-text table 3.2-8: Yearly conditional risk per 1000 patients for Cohort 3
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	Agranulocytosis					Severe Leukopenia				
	# of occur.	Cond. risk	Std. Error	Lower 95% C.L.	Upper 95% C.L.	# of occur.	Cond. risk	Std. Error	Lower 95% C.L.	Upper 95% C.L.
Yr. 0-1	54	1.955	0.266	1.434	2.476	52	1.882	0.261	1.371	2.394
0.5-1.5	9	0.534	0.178	0.185	0.883	5	0.297	0.133	0.037	0.557
1-2	2	0.168	0.119	0.000	0.400	1	0.084	0.084	0.000	0.248
2-3	0	0.000	0.000	0.000	0.000	4	0.759	0.379	0.015	1.502
3-4	0	0.000	0.000	0.000	0.000	0	0.000	0.000	0.000	0.000

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                                        Post-text table 3.3-1a
                          Summary statistics for incidence of severe leukopenia [1]
                                            All duration
                          With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                           (Excluding patient's data met criteria 1, 2, and 3) [2]

_____

Cohort                                   Category                                  All Duration
_____

Cohort 1                                 Incidence/1000 patient year                      1.432
                                         Number of incidence                                458
                                         Number of patient                                97485
                                         Total patient year                              319909

Cohort 2                                 Incidence/1000 patient year                      1.966
                                         Number of incidence                                 94
                                         Number of patient                                41359
                                         Total patient year                               47815


Cohort 3                                 Incidence/1000 patient year                      1.385
                                         Number of incidence                                 57
                                         Number of patient                                39260
                                         Total patient year                               41167

_____
[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.



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                                Post-text table 3.3-1a (Continued)
                        Summary statistics for incidence of severe leukopenia [1]
                                            All duration
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                         (Excluding patient's data met criteria 1, 2, and 3) [2]

_____

Cohort                                      Category                              All Duration
_____

Cohorts 1 and 2                             Incidence/1000 patient year                  1.501
                                            Number of incidence                            552
                                            Number of patient                           138844
                                            Total patient year                          367724

Cohorts 1, 2, and 3                         Incidence/1000 patient year                  1.489
                                            Number of incidence                            609
                                            Number of patient                           178104
                                            Total patient year                          408891

_____
[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.




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Post-text table 3.3-1b
Summary statistics for incidence of severe leukopenia [1]
By duration of 1 - 6 months and > 6 months
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
(Excluding patient's data met criteria 1, 2, and 3) [2]

_____

Cohort	Category	(1 - 6] Months	> 6 Months
		------------- Duration -------------	
Cohort 1	Incidence/1000 patient year	7.708	0.492
	Number of incidence	321	137
	Number of patient	97485	75630
	Total patient year	41644	278265
Cohort 2	Incidence/1000 patient year	4.966	0.383
	Number of incidence	82	12
	Number of patient	41359	28670
	Total patient year	16512	31304
Cohort 3	Incidence/1000 patient year	3.392	0.333
	Number of incidence	48	9
	Number of patient	39260	22204
	Total patient year	14149	27017

_____

[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
          will be excluded after the first generic clozapine.

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                              Post-text table 3.3-1b (Continued)
                        Summary statistics for incidence of severe leukopenia [1]
                              By duration of 1 - 6 months and > 6 months
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                         (Excluding patient's data met criteria 1, 2, and 3) [2]
```

_____

Cohort	Category	------------- Duration -------------	
		(1 - 6] Months	> 6 Months
Cohorts 1 and 2	Incidence/1000 patient year	6.930	0.481
	Number of incidence	403	149
	Number of patient	138844	104300
	Total patient year	58156	309569
Cohorts 1, 2, and 3	Incidence/1000 patient year	6.237	0.469
	Number of incidence	451	158
	Number of patient	178104	126504
	Total patient year	72305	336586

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[1] Severe leukopenia is defined as WBC counts < 2000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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                                      Post-text table 3.3-1c
                        Summary statistics for incidence of severe leukopenia [1]
                             By duration of 1 - 18, 19 - 52, and > 52 weeks
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                         (Excluding patient's data meeting criteria 1, 2, and 3) [2]


_____

                                                 ------------------------ Duration ------------------------
Cohort                    Category                 (0-18] Weeks            (18-52] Weeks          >52 Weeks
_____

Cohort 1                  Incidence/1000 patient year        9.801                 1.156              0.458
                          Number of incidence                292                     55                111
                          Number of patient                97485                  79023              68527
                          Total patient year               29794                  47595             242519

Cohort 2                  Incidence/1000 patient year        6.434                 0.658              0.314
                          Number of incidence                 77                     11                  6
                          Number of patient                41359                  30673              20847
                          Total patient year               11968                  16715              19132

Cohort 3                  Incidence/1000 patient year        4.082                 0.693              0.283
                          Number of incidence                 43                      9                  5
                          Number of patient                39260                  25085              15935
                          Total patient year               10534                  12994              17639

_____
[1] Severe Leukopenia is defined as WBC counts < 2000/mm2.
[2] Criteria 1: Excluded patients with only one record of WBC;

    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.


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                              Post-text table 3.3-1c (Continued)
                     Summary statistics for incidence of severe leukopenia [1]
                          By duration of 1 - 18, 19 - 52, and > 52 weeks
                     With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                      (Excluding patient's data meeting criteria 1, 2, and 3) [2]
```
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Cohort	Category	------------------------ Duration ------------------------		
		(0-18] Weeks	(18-52] Weeks	>52 Weeks
Cohorts 1 and 2	Incidence/1000 patient year	8.836	1.026	0.447
	Number of incidence	369	66	117
	Number of patient	138844	109696	89374
	Total patient year	41762	64311	261651
Cohorts 1, 2, and 3	Incidence/1000 patient year	7.878	0.970	0.437
	Number of incidence	412	75	122
	Number of patient	178104	134781	105309
	Total patient year	52296	77305	279290

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[1] Severe Leukopenia is defined as WBC counts < 2000/mm2.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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Post-text table 3.3-2: Life table for incidence of severe leukopenia for Cohorts 1 & 2
with data cut-off date of 1-Apr-1998
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	403	403	138844	0.0000	0.0000	0.0000	6.6298	5.9825	7.2771
0.5-1	32	435	104300	3.3094	2.9869	3.6320	0.6609	0.4319	0.8899
1-2	36	471	89374	3.6387	3.2967	3.9808	0.4517	0.3042	0.5993
2-3	26	497	70013	4.0887	3.7166	4.4609	0.4173	0.2569	0.5778
3-4	20	517	54587	4.5043	4.0994	4.9091	0.4137	0.2324	0.5950
4-5	15	532	42107	4.9160	4.4729	5.3590	0.4246	0.2097	0.6394
5-6	11	543	28555	5.3384	4.8466	5.8301	0.4925	0.2015	0.7836
6-7	5	548	16111	5.8282	5.2578	6.3985	0.4331	0.0535	0.8128
7-8	4	552	6976	6.2587	5.5751	6.9423	0.9322	0.0187	1.8457
8-9	0	552	1606	7.1846	6.0492	8.3200	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.3-3: Life table for incidence of severe leukopenia for Cohort 3

'

(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	48	48	39260	0.0000	0.0000	0.0000	3.1238	2.2401	4.0075
0.5-1	4	52	22204	1.5607	1.1195	2.0018	0.4195	0.0084	0.8306
1-2	1	53	15935	1.7701	1.2836	2.2565	0.0839	0.0000	0.2483
2-3	4	57	7903	1.8538	1.3405	2.3672	0.7589	0.0152	1.5027
3-4	0	57	2638	2.6111	1.7092	3.5130	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.3-4: Life table for incidence of severe leukopenia for all 3 Cohorts
with data cut-off date of 1-Apr-1998 for Cohorts 1 & 2
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	451	451	178104	0.0000	0.0000	0.0000	5.9224	5.3758	6.4689
0.5-1	36	487	126504	2.9568	2.6843	3.2293	0.6212	0.4183	0.8241
1-2	37	524	105309	3.2664	2.9759	3.5570	0.4039	0.2737	0.5340
2-3	30	554	77916	3.6689	3.3508	3.9870	0.4440	0.2851	0.6029
3-4	20	574	57225	4.1112	3.7560	4.4663	0.4027	0.2262	0.5792
4-5	15	589	42107	4.5121	4.1160	4.9082	0.4246	0.2097	0.6394
5-6	11	600	28555	4.9347	4.4847	5.3846	0.4925	0.2015	0.7836
6-7	5	605	16111	5.4247	4.8898	5.9595	0.4331	0.0535	0.8128
7-8	4	609	6976	5.8554	5.2009	6.5098	0.9322	0.0187	1.8457
8-9	0	609	1606	6.7817	5.6633	7.9000	0.0000	-	-

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

```
                                Post-text table 3.3-5
                   Summary statistics for incidence of severe leukopenia [1]
                                    By calendar year
                  With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                     (Excluding patient's data met criteria 1, 2, and 3) [2]
```

Cohort: Cohorts 1 and 2
_____

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of new patients started Clozaril	9639.0	13763.0	22024.0	25444.0	19750.0	19603.0	19195.0	9426.0	0.0
% of new patients [3]	100.0	61.7	53.8	41.7	27.3	24.9	22.1	11.5	0.0
Number of patients taking drug during the year	9639.0	22290.0	40926.0	60992.0	72330.0	78742.0	86799.0	81864.0	68123.0
Patient year	4462.7	13074.5	27357.4	44138.5	55718.8	63474.6	72097.9	70877.5	16522.4
Number of severe leukopenia	38.0	75.0	107.0	86.0	56.0	67.0	77.0	40.0	6.0
Rate of severe leukopenia / 1000 patients	3.9	3.4	2.6	1.4	0.8	0.9	0.9	0.5	0.1
Incidence / 1000 patient year	8.5	5.7	3.9	1.9	1.0	1.1	1.1	0.6	0.4

_____

[1] Severe leukopenia is defined as WBC counts < 1000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                              Post-text table 3.3-5 (Continued)
                     Summary statistics for incidence of severe leukopenia [1]
                                      By calendar year
                     With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                       (Excluding patient's data met criteria 1, 2, and 3) [2]
```

Cohort: Cohort 3
_____

Category	1997	1998	1999	2000	2001
Number of new patients started Clozaril	3206.0	12602.0	11786.0	8186.0	3480.0
% of new patients [3]	100.0	82.3	53.2	36.8	21.0
Number of patients taking drug during the year	3206.0	15313.0	22156.0	22263.0	16572.0
Patient year	386.7	6852.1	13051.3	13966.0	6910.7
Number of severe leukopenia	1.0	21.0	21.0	10.0	4.0
Rate of severe leukopenia / 1000 patients	0.3	1.4	0.9	0.4	0.2
Incidence / 1000 patient year	2.6	3.1	1.6	0.7	0.6

_____
[1] Severe leukopenia is defined as WBC counts < 1000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                             Post-text table 3.3-6
                 Summary statistics for incidence of severe leukopenia [1]
                               After 6 month treatment
                                 By calendar year
               With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
```

Cohort: Cohorts 1 and 2

_____

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of patients taking drug during the year	4272.0	12840.0	27232.0	44495.0	58020.0	65225.0	74617.0	75785.0	67979.0
Patient year	1074.0	7659.8	18176.2	33505.7	47170.0	55543.9	63940.7	66268.1	16230.0
Number of severe leukopenia	1.0	7.0	18.0	16.0	18.0	27.0	34.0	22.0	6.0
Rate of severe leukopenia / 1000 patients	0.2	0.5	0.7	0.4	0.3	0.4	0.5	0.3	0.1
Incidence / 1000 patient year	0.9	0.9	1.0	0.5	0.4	0.5	0.5	0.3	0.4

_____

[1] Severe leukopenia is defined as WBC counts < 1000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                              Post-text table 3.3-6 (Continued)
                        Summary statistics for incidence of severe leukopenia [1]
                                      After 6 month treatment
                                        By calendar year
                        With data cut-off date of 01-Apr-1998 for cohorts 1 and 2


Cohort: Cohort 3
_____

Category               1998      1999      2000      2001
_____


Number of patients    6328.0   13763.0   15828.0   12749.0
taking drug during
the year
Patient year          2201.3    8321.7   10837.2    5657.2


Number of severe         0.0       4.0       1.0       4.0
leukopenia
Rate of severe           0.0       0.3       0.1       0.3
leukopenia / 1000
patients
Incidence / 1000         0.0       0.5       0.1       0.7
patient year


_____
[1] Severe leukopenia is defined as WBC counts < 1000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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                                    Post-text table 3.4-1a
                       Summary statistics for incidence of moderate leukopenia [1]
                                          All duration
                       With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                        (Excluding patient's data meeting criteria 1, 2, and 3) [2]


_____

Cohort                                  Category                                All Duration
_____

Cohort 1                                Incidence/1000 patient year                   11.699
                                        Number of incidence                            3673
                                        Number of patient                             97485
                                        Total patient year                           313963

Cohort 2                                Incidence/1000 patient year                   17.116
                                        Number of incidence                             811
                                        Number of patient                             41359
                                        Total patient year                            47383

Cohort 3                                Incidence/1000 patient year                   14.881
                                        Number of incidence                             608
                                        Number of patient                             39260
                                        Total patient year                            40858

_____

[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.



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                              Post-text table 3.4-1a (Continued)
                     Summary statistics for incidence of moderate leukopenia [1]
                                          All duration
                   With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                    (Excluding patient's data meeting criteria 1, 2, and 3) [2]
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Cohort	Category	All Duration
Cohorts 1 and 2	Incidence/1000 patient year	12.409
	Number of incidence	4484
	Number of patient	138844
	Total patient year	361346
Cohorts 1, 2, and 3	Incidence/1000 patient year	12.660
	Number of incidence	5092
	Number of patient	178104
	Total patient year	402204

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```
[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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                                Post-text table 3.4-1b
                  Summary statistics for incidence of moderate leukopenia [1]
                        By duration of 1 - 6 months and > 6 months
                  With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                   (Excluding patient's data met criteria 1, 2, and 3) [2]


_____

                                                       ------------- Duration -------------

Cohort                          Category               (1 - 6] Months        > 6 Months
_____

Cohort 1                        Incidence/1000 patient year       31.008            8.760
                                Number of incidence                1286             2387
                                Number of patient                 97485            75117
                                Total patient year                41473           272491

Cohort 2                        Incidence/1000 patient year       29.921           10.311
                                Number of incidence                 492              319
                                Number of patient                 41359            28447
                                Total patient year                16444            30939

Cohort 3                        Incidence/1000 patient year       27.958            7.996
                                Number of incidence                 394              214
                                Number of patient                 39260            22071
                                Total patient year                14093            26765

_____
[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.



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                          Post-text table 3.4-1b (Continued)
                 Summary statistics for incidence of moderate leukopenia [1]
                        By duration of 1 - 6 months and > 6 months
                 With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                   (Excluding patient's data met criteria 1, 2, and 3) [2]
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| Cohort | Category | ------------ Duration ------------ | |
		(1 - 6] Months	> 6 Months
Cohorts 1 and 2	Incidence/1000 patient year	30.700	8.918
	Number of incidence	1778	2706
	Number of patient	138844	103564
	Total patient year	57916	303430
Cohorts 1, 2, and 3	Incidence/1000 patient year	30.163	8.843
	Number of incidence	2172	2920
	Number of patient	178104	125635
	Total patient year	72009	330195

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```
[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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                              Post-text table 3.4-1c
                 Summary statistics for incidence of moderate leukopenia [1]
                     By duration of 1 - 18, 19 - 52, and > 52 weeks
                  With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                   (Excluding patient's data meeting criteria 1, 2, and 3) [2]
```
_____

Cohort	Category	------------------------ Duration ------------------------		
		(0-18] Weeks	(18-52] Weeks	>52 Weeks

Cohort	Category	(0-18] Weeks	(18-52] Weeks	>52 Weeks
Cohort 1	Incidence/1000 patient year	36.436	13.150	8.311
	Number of incidence	1082	621	1970
	Number of patient	97485	78577	67828
	Total patient year	29696	47224	237043
Cohort 2	Incidence/1000 patient year	32.520	15.810	8.527
	Number of incidence	388	262	161
	Number of patient	41359	30497	20621
	Total patient year	11931	16572	18880
Cohort 3	Incidence/1000 patient year	32.864	10.618	7.218
	Number of incidence	345	137	126
	Number of patient	39260	24951	15797
	Total patient year	10498	12903	17457

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```
[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm2.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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Clozaril (clozapine)

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Post-text table 3.4-1c (Continued)
Summary statistics for incidence of moderate leukopenia [1]
By duration of 1 - 18, 19 - 52, and > 52 weeks
With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
(Excluding patient's data meeting criteria 1, 2, and 3) [2]

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Cohort	Category	(0-18] Weeks	(18-52] Weeks	>52 Weeks
Cohorts 1 and 2	Incidence/1000 patient year	35.314	13.841	8.327
	Number of incidence	1470	883	2131
	Number of patient	138844	109074	88449
	Total patient year	41627	63796	255923
Cohorts 1, 2, and 3	Incidence/1000 patient year	34.821	13.299	8.256
	Number of incidence	1815	1020	2257
	Number of patient	178104	134025	104246
	Total patient year	52124	76699	273380

_____

[1] Moderate Leukopenia is defined as WBC counts <= 3000/mm2.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
               will be excluded after the first generic clozapine.

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Post-text table 3.4-2: Life table for incidence of moderate leukopenia for Cohorts 1 & 2
with data cut-off date of 1-Apr-1998
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	1778	1778	138844	0.0000	0.0000	0.0000	29.3390	27.9753	30.7027
0.5-1	575	2353	103564	14.5627	13.8907	15.2346	11.9784	10.9993	12.9574
1-2	728	3081	88449	20.4470	19.6248	21.2693	9.2553	8.5830	9.9276
2-3	493	3574	68866	29.4713	28.4276	30.5151	8.0640	7.3522	8.7758
3-4	371	3945	53406	37.2662	36.0246	38.5079	7.8608	7.0609	8.6606
4-5	246	4191	40987	44.8044	43.3548	46.2540	7.1668	6.2712	8.0624
5-6	172	4363	27663	51.6256	49.9545	53.2968	7.9663	6.7758	9.1568
6-7	86	4449	15519	59.1507	57.1498	61.1515	7.7446	6.1078	9.3814
7-8	32	4481	6690	66.4091	63.9037	68.9145	7.7897	5.0908	10.4886
8-9	3	4484	1526	73.6533	70.1275	77.1790	3.9318	0.0000	8.3811

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.4-3: Life table for incidence of moderate leukopenia for Cohort 3

(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	394	394	39260	0.0000	0.0000	0.0000	25.6966	23.1594	28.2339
0.5-1	88	482	22071	12.7663	11.5138	14.0188	9.2954	7.3533	11.2376
1-2	77	559	15797	17.3441	15.7741	18.9140	6.5240	5.0669	7.9812
2-3	41	600	7808	23.7341	21.6230	25.8452	7.8710	5.4617	10.2802
3-4	8	608	2610	31.3882	28.2524	34.5239	6.1303	1.8823	10.3782

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

Post-text table 3.4-4: Life table for incidence of moderate leukopenia for all 3 Cohorts
with data cut-off date of 1-Apr-1998 for Cohorts 1 & 2
(Excluded patients data meeting criteria 1, 2, 3)

Time interval	# of occurrences	Cumulative # of occurrences	# of patients left	Cumulative rate /1000 pat.	Cum. rate /1000 pat. 95% L.C.L.	Cum. rate /1000 pat. 95% U.C.L.	Hazard rate/ 1000 pt-yr	Hazard/ 1000 pt-yr 95% L.C.L.	Hazard/ 1000 pt-yr 95% L.C.L.
Yr. 0-0.5	2172	2172	178104	0.0000	0.0000	0.0000	28.6035	27.4006	29.8064
0.5-1	663	2835	125635	14.2002	13.6073	14.7931	11.5364	10.6583	12.4145
1-2	805	3640	104246	19.8701	19.1403	20.6000	8.8990	8.2842	9.5137
2-3	534	4174	76674	28.5536	27.6156	29.4917	8.0488	7.3662	8.7315
3-4	379	4553	56016	36.3413	35.2017	37.4809	7.8142	7.0275	8.6009
4-5	246	4799	40987	43.8422	42.4841	45.2003	7.1668	6.2712	8.0624
5-6	172	4971	27663	50.6703	49.0763	52.2644	7.9663	6.7758	9.1568
6-7	86	5057	15519	58.2030	56.2644	60.1415	7.7446	6.1078	9.3814
7-8	32	5089	6690	65.4687	63.0110	67.9263	7.7897	5.0908	10.4886
8-9	3	5092	1526	72.7201	69.2258	76.2144	3.9318	0.0000	8.3811

Note: L.C.L = Lower Confidence Limit;   U.C.L = Upper Confidence Limit

```
                                       Post-text table 3.4-5
                        Summary statistics for incidence of moderate leukopenia [1]
                                          By calendar year
                       With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                        (Excluding patient's data met criteria 1, 2, and 3) [2]
```

Cohort: Cohorts 1 and 2

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of new patients started Clozaril	9639.0	13763.0	22024.0	25444.0	19750.0	19603.0	19195.0	9426.0	0.0
% of new patients [3]	100.0	62.0	54.1	42.0	27.6	25.2	22.4	11.7	0.0
Number of patients taking drug during the year	9639.0	22209.0	40744.0	60649.0	71681.0	77779.0	85533.0	80316.0	66369.0
Patient year	4433.0	12945.3	27099.0	43657.0	54898.1	62357.7	70657.2	69217.9	16081.0
Number of moderate leukopenia	165.0	310.0	415.0	604.0	703.0	652.0	777.0	673.0	185.0
Rate of moderate leukopenia / 1000 patients	17.1	14.0	10.2	10.0	9.8	8.4	9.1	8.4	2.8
Incidence / 1000 patient year	37.2	23.9	15.3	13.8	12.8	10.5	11.0	9.7	11.5

[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
   Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
   Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
              will be excluded after the first generic clozapine.

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                            Post-text table 3.4-5 (Continued)
                  Summary statistics for incidence of moderate leukopenia [1]
                                      By calendar year
                  With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
                    (Excluding patient's data met criteria 1, 2, and 3) [2]
```

Cohort: Cohort 3

_____

Category	1997	1998	1999	2000	2001
Number of new patients started Clozaril	3206.0	12602.0	11786.0	8186.0	3480.0
% of new patients [3]	100.0	82.3	53.4	36.9	21.2
Number of patients taking drug during the year	3206.0	15304.0	22091.0	22165.0	16451.0
Patient year	385.8	6817.2	12962.4	13849.1	6843.0
Number of moderate leukopenia	12.0	153.0	197.0	169.0	77.0
Rate of moderate leukopenia / 1000 patients	3.7	10.0	8.9	7.6	4.7
Incidence / 1000 patient year	31.1	22.4	15.2	12.2	11.3

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[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                              Post-text table 3.4-6
                Summary statistics for incidence of moderate leukopenia [1]
                              After 6 months treatment
                                 By calendar year
                With data cut-off date of 01-Apr-1998 for cohorts 1 and 2
```

Cohort: Cohorts 1 and 2
_____

Category	1990	1991	1992	1993	1994	1995	1996	1997	1998
Number of patients taking drug during the year	4230.0	12713.0	26996.0	44074.0	57296.0	64200.0	73268.0	74181.0	66221.0
Patient year	1063.3	7557.4	17948.8	33059.4	46388.7	54455.8	62532.9	64633.3	15790.4
Number of moderate leukopenia	11.0	99.0	144.0	312.0	460.0	447.0	523.0	532.0	178.0
Rate of moderate leukopenia / 1000 patients	2.6	7.8	5.3	7.1	8.0	7.0	7.1	7.2	2.7
Incidence / 1000 patient year	10.3	13.1	8.0	9.4	9.9	8.2	8.4	8.2	11.3

_____
[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.

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                              Post-text table 3.4-6 (Continued)
                      Summary statistics for incidence of moderate leukopenia [1]
                                    After 6 months treatment
                                      By calendar year
                      With data cut-off date of 01-Apr-1998 for cohorts 1 and 2


Cohort: Cohort 3
_____

Category              1998     1999     2000     2001

_____


Number of patients    6294.0  13664.0  15710.0  12629.0
taking drug during
the year
Patient year          2185.8   8254.4  10732.1   5592.4


Number of moderate      18.0     62.0     86.0     48.0
leukopenia
Rate of moderate         2.9      4.5      5.5      3.8
leukopenia / 1000
patients
Incidence / 1000         8.2      7.5      8.0      8.6
patient year


_____
[1] Moderate leukopenia is defined as WBC counts <= 3000/mm^3.
[2] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data
                will be excluded after the first generic clozapine.
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Post-text table 3.5-1
Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
With patients discontinued before 1-Apr-1998 for cohorts 1 and 2
(Excluding patients data meeting criteria 1, 2, and 3) [1]

_____

Cohort	Statistics	<= 6 months	> 6 months	All
Cohort 1	N	32629	33285	65914
	Mean	8594.1	8467.0	8529.9
	5th percentile	4800.0	5000.0	4900.0
	25th percentile	6400.0	6500.0	6500.0
	Median	7900.0	7900.0	7900.0
	75th percentile	9700.0	9700.0	9700.0
	95th percentile	13400.0	13200.0	13300.0
Cohort 2	N	16691	6161	22852
	Mean	7982.0	8059.1	8002.8
	5th percentile	4700.0	4700.0	4700.0
	25th percentile	6200.0	6300.0	6200.0
	Median	7600.0	7700.0	7600.0
	75th percentile	9300.0	9400.0	9300.0
	95th percentile	12800.0	12600.0	12700.0

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.

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Post-text table 3.5-1 (Continued)
Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
With patients discontinued before 1-Apr-1998 for cohorts 1 and 2
(Excluding patients data meeting criteria 1, 2, and 3) [1]

_____

Cohort	Statistics	<= 6 months	> 6 months	All
Cohort 3	N	18563	3330	21893
	Mean	7867.6	7983.2	7885.1
	5th percentile	4600.0	4800.0	4600.0
	25th percentile	6100.0	6200.0	6100.0
	Median	7400.0	7600.0	7500.0
	75th percentile	9100.0	9300.0	9100.0
	95th percentile	12400.0	12300.0	12400.0
Cohorts 1 and 2	N	49320	39446	88766
	Mean	8386.9	8403.3	8394.2
	5th percentile	4800.0	4900.0	4800.0
	25th percentile	6300.0	6500.0	6400.0
	Median	7800.0	7900.0	7800.0
	75th percentile	9600.0	9700.0	9600.0
	95th percentile	13200.0	13200.0	13200.0

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
            after the first generic clozapine.

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                                                    Post-text table 3.5-2
                        Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                                 For patients with 3000<= WBC <= 6000 at time of discontinuation
                                 With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

_____

Cohort                      Statistics                 <= 6 months            > 6 months             All
_____

Cohort 1                    N                           6053                   5793                   11846
                            Mean                         5188.9                 5241.8                 5214.8
                            5th percentile               3900.0                 4000.0                 4000.0
                            25th percentile              4800.0                 4900.0                 4800.0
                            Median                       5300.0                 5400.0                 5300.0
                            75th percentile              5700.0                 5700.0                 5700.0
                            95th percentile              6000.0                 6000.0                 6000.0

Cohort 2                    N                           3784                   1291                   5075
                            Mean                         5173.4                 5208.6                 5182.4
                            5th percentile               3900.0                 4000.0                 4000.0
                            25th percentile              4800.0                 4800.0                 4800.0
                            Median                       5300.0                 5300.0                 5300.0
                            75th percentile              5700.0                 5700.0                 5700.0
                            95th percentile              6000.0                 6000.0                 6000.0

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.



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                               Post-text table 3.5-2 (Continued)
            Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                      For patients with 3000<= WBC <= 6000 at time of discontinuation
                      With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

_____

Cohort                  Statistics              <= 6 months          > 6 months            All
_____

Cohort 3                N                          4396                 712                5108
                        Mean                       5165.1               5185.2             5167.9
                        5th percentile             4000.0               3900.0             3900.0
                        25th percentile            4700.0               4800.0             4800.0
                        Median                     5300.0               5300.0             5300.0
                        75th percentile            5700.0               5700.0             5700.0
                        95th percentile            6000.0               6000.0             6000.0

Cohorts 1 and 2         N                          9837                 7084               16921
                        Mean                       5182.9               5235.8             5205.1
                        5th percentile             3900.0               4000.0             4000.0
                        25th percentile            4800.0               4900.0             4800.0
                        Median                     5300.0               5400.0             5300.0
                        75th percentile            5700.0               5700.0             5700.0
                        95th percentile            6000.0               6000.0             6000.0
_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.



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                                     Post-text table 3.5-3a
              Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                       For patients with 3000<= WBC <= 4000 at time of discontinuation
                       With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

_____

Cohort                  Statistics              <= 6 months          > 6 months           All
_____

Cohort 1                N                           410                  304               714
                        Mean                       3702.3               3708.0            3704.7
                        5th percentile             3100.0               3200.0            3100.0
                        25th percentile            3500.0               3500.0            3500.0
                        Median                     3800.0               3800.0            3800.0
                        75th percentile            3900.0               3900.0            3900.0
                        95th percentile            4000.0               4000.0            4000.0

Cohort 2                N                           239                   72               311
                        Mean                       3713.4               3737.5            3719.0
                        5th percentile             3100.0               3300.0            3200.0
                        25th percentile            3600.0               3600.0            3600.0
                        Median                     3800.0               3800.0            3800.0
                        75th percentile            3900.0               4000.0            3900.0
                        95th percentile            4000.0               4000.0            4000.0

_____

[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.



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                               Post-text table 3.5-3a (Continued)
            Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                     For patients with 3000<= WBC <= 4000 at time of discontinuation
                     With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

_____

Cohort                    Statistics              <= 6 months        > 6 months           All
_____

Cohort 3                  N                            284                50              334
                          Mean                        3710.3             3786.0          3721.6
                          5th percentile              3200.0             3400.0          3200.0
                          25th percentile             3500.0             3600.0          3600.0
                          Median                      3800.0             3800.0          3800.0
                          75th percentile             3900.0             3900.0          3900.0
                          95th percentile             4000.0             4000.0          4000.0

Cohorts 1 and 2           N                            649                376            1025
                          Mean                        3706.4             3713.6          3709.0
                          5th percentile              3100.0             3200.0          3200.0
                          25th percentile             3500.0             3500.0          3500.0
                          Median                      3800.0             3800.0          3800.0
                          75th percentile             3900.0             3900.0          3900.0
                          95th percentile             4000.0             4000.0          4000.0

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.



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                                    Post-text table 3.5-3b
            Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                      For patients with 4000< WBC <= 5000 at time of discontinuation
                     With patients discontinued before 1-Apr-1998 for cohorts 1 and 2
```
_____

Cohort	Statistics	<= 6 months	> 6 months	All
Cohort 1	N	1768	1561	3329
	Mean	4643.3	4652.2	4647.4
	5th percentile	4160.0	4100.0	4100.0
	25th percentile	4400.0	4500.0	4400.0
	Median	4700.0	4700.0	4700.0
	75th percentile	4900.0	4900.0	4900.0
	95th percentile	5000.0	5000.0	5000.0
Cohort 2	N	1187	374	1561
	Mean	4635.8	4601.3	4627.5
	5th percentile	4100.0	4100.0	4100.0
	25th percentile	4400.0	4400.0	4400.0
	Median	4700.0	4600.0	4700.0
	75th percentile	4900.0	4800.0	4900.0
	95th percentile	5000.0	5000.0	5000.0

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```
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
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                                     Post-text table 3.5-3b (Continued)
                  Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                           For patients with 4000< WBC <= 5000 at time of discontinuation
                           With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

_____

Cohort                        Statistics                 <= 6 months         > 6 months           All
_____

Cohort 3                      N                              1387                216             1603
                              Mean                           4627.6             4667.1            4632.9
                              5th percentile                 4100.0             4100.0            4100.0
                              25th percentile                4400.0             4500.0            4400.0
                              Median                         4700.0             4700.0            4700.0
                              75th percentile                4900.0             4900.0            4900.0
                              95th percentile                5000.0             5000.0            5000.0

Cohorts 1 and 2               N                              2955                1935             4890
                              Mean                           4640.3             4642.3            4641.1
                              5th percentile                 4100.0             4100.0            4100.0
                              25th percentile                4400.0             4400.0            4400.0
                              Median                         4700.0             4700.0            4700.0
                              75th percentile                4900.0             4900.0            4900.0
                              95th percentile                5000.0             5000.0            5000.0

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.




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                                          Post-text table 3.5-3c
                  Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                          For patients with 5000< WBC <= 6000 at time of discontinuation
                          With patients discontinued before 1-Apr-1998 for cohorts 1 and 2

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Cohort                   Statistics               <= 6 months            > 6 months              All
_____

Cohort 1                 N                         3875                   3928                    7803
                         Mean                      5595.1                 5594.9                  5595.0
                         5th percentile            5100.0                 5100.0                  5100.0
                         25th percentile           5400.0                 5400.0                  5400.0
                         Median                    5600.0                 5600.0                  5600.0
                         75th percentile           5800.0                 5800.0                  5800.0
                         95th percentile           6000.0                 6000.0                  6000.0

Cohort 2                 N                         2358                    845                    3203
                         Mean                      5592.1                 5602.7                  5594.9
                         5th percentile            5100.0                 5100.0                  5100.0
                         25th percentile           5400.0                 5400.0                  5400.0
                         Median                    5600.0                 5600.0                  5600.0
                         75th percentile           5800.0                 5900.0                  5800.0
                         95th percentile           6000.0                 6000.0                  6000.0

_____
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.




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                                  Post-text table 3.5-3c (Continued)
              Summary statistics of WBC counts at discontinuation by cohort and duration of treatment
                        For patients with 5000< WBC <= 6000 at time of discontinuation
                        With patients discontinued before 1-Apr-1998 for cohorts 1 and 2
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Cohort	Statistics	<= 6 months	> 6 months	All
Cohort 3	N	2725	446	3171
	Mean	5590.4	5592.9	5590.7
	5th percentile	5100.0	5100.0	5100.0
	25th percentile	5300.0	5400.0	5400.0
	Median	5600.0	5600.0	5600.0
	75th percentile	5800.0	5800.0	5800.0
	95th percentile	6000.0	6000.0	6000.0
Cohorts 1 and 2	N	6233	4773	11006
	Mean	5594.0	5596.2	5595.0
	5th percentile	5100.0	5100.0	5100.0
	25th percentile	5400.0	5400.0	5400.0
	Median	5600.0	5600.0	5600.0
	75th percentile	5800.0	5800.0	5800.0
	95th percentile	6000.0	6000.0	6000.0

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```
[1] Criteria 1: Excluded patients with only one record of WBC;
    Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril;
    Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 1997. All data will be excluded
                after the first generic clozapine.
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Post-text table 3.5-4
Kaplan-Meier estimate of probability of discontinuation
With data cut-off date of 1-Apr-1998 for cohorts 1 and 2

Days on Treatment	-------- Probability of discontinuation (%) --------	
	Cohorts 1 and 2	Cohort 3
0	0.00	0.00
1	7.09	10.02
2	7.16	10.17
3	7.23	10.28
4	7.32	10.40
5	7.48	10.69
6	7.71	11.08
7	8.15	11.79
8	9.83	14.62
9	10.20	15.32
10	10.42	15.74
11	10.62	16.14
12	10.83	16.57
13	11.12	17.12
14	11.56	17.79
21	14.33	22.21
28	16.63	25.95
35	18.58	29.11
42	20.24	32.07
49	21.70	34.40
56	23.06	36.47
63	24.35	38.38
70	25.56	40.28
77	26.71	41.87
84	27.83	43.43
91	28.87	44.84
98	29.90	46.19

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                            Post-text table 3.5-4 (Continued)
                     Kaplan-Meier estimate of probability of discontinuation
                     With data cut-off date of 1-Apr-1998 for cohorts 1 and 2

                    Days on   -------- Probability of discontinuation (%) --------
                    Treatment   Cohorts 1 and 2   Cohort 3
_____

                      105   30.87   47.61
                      112   31.77   48.95
                      119   32.67   50.20
                      126   33.54   51.28
                      133   34.42   52.48
                      140   35.19   53.69
                      147   35.96   54.55
                      154   36.74   55.56
                      161   37.43   56.48
                      168   38.12   57.09
                      175   38.82   57.36
                      182   39.51   57.65
                      196   40.80   58.23
                      210   42.03   58.84
                      224   43.25   59.48
                      238   44.39   60.17
                      252   45.45   60.72
                      266   46.49   61.37
                      280   47.50   61.86
                      294   48.42   62.42
                      308   49.32   63.08
                      322   50.13   63.69
                      336   50.99   64.20
                      350   51.73   64.75
                      364   52.49   65.27
                      378   53.28   65.81
                      392   54.02   66.37

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Post-text table 3.5-4 (Continued)
Kaplan-Meier estimate of probability of discontinuation
With data cut-off date of 1-Apr-1998 for cohorts 1 and 2

Days on Treatment	-------- Probability of discontinuation (%) --------	
	Cohorts 1 and 2	Cohort 3
406	54.77	66.88
420	55.48	67.49
434	56.21	67.96
448	56.86	68.46
462	57.55	68.98
476	58.20	69.47
490	58.81	69.89
504	59.41	70.40
518	59.98	70.78
532	60.60	71.16
546	61.17	71.57
560	61.73	71.98
574	62.25	72.29
588	62.70	72.73
602	63.27	73.12
616	63.80	73.55
630	64.30	73.96
644	64.77	74.28
658	65.26	74.64
672	65.72	74.93
686	66.18	75.35
700	66.61	75.70
714	67.04	75.93
728	67.45	76.30
742	67.82	76.58
756	68.25	76.91
770	68.65	77.21

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                          Post-text table 3.5-4 (Continued)
                  Kaplan-Meier estimate of probability of discontinuation
                  With data cut-off date of 1-Apr-1998 for cohorts 1 and 2

        Days on   -------- Probability of discontinuation (%) --------
        Treatment   Cohorts 1 and 2   Cohort 3
_____

             784   69.07   77.55
             798   69.52   77.81
             812   69.89   78.14
             826   70.25   78.51
             840   70.64   78.86
             854   71.00   79.06
             868   71.38   79.24
             882   71.72   79.46
             896   72.06   79.74
             910   72.41   79.86
             924   72.72   79.96
             938   73.06   80.25
             952   73.38   80.48
             966   73.70   80.66
             980   74.00   80.82
             994   74.28   80.95
            1008   74.61   81.20
            1022   74.90   81.41
            1036   75.20   81.65
            1050   75.46   81.89
            1064   75.70   82.02

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Post-text table 3.6-1
Summary statistics on duration of prodrome and slope during prodrome for patients
who developed moderate leukopenia by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 1 & 2	<= 6 months	n	1778.0	1778.0
		mean	22.8	325.5
		std	14.9	1171.3
		median	21.0	170.2
		25th percentile	13.0	83.5
		75th percentile	31.0	321.4
		min	0.0	-43.6
		max	105.0	41100.0
	6 months to 1 year	n	582.0	582.0
		mean	23.3	371.1
		std	15.6	1138.6
		median	21.0	140.2
		25th percentile	13.0	76.1
		75th percentile	29.0	333.1
		min	0.0	0.0
		max	119.0	24600.0
	1-2 years	n	775.0	775.0
		mean	24.6	346.7
		std	16.8	579.4
		median	21.0	161.4
		25th percentile	14.0	73.8
		75th percentile	34.0	387.0
		min	0.0	-1.0

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
          be excluded after the first generic clozapine
     + Slope = rate of decrease of WBC (count/day) during prodrome

Post-text table 3.6-1 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for patients
who developed moderate leukopenia by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 1 & 2	1-2 years	max	140.0	8766.7
	> 2 years	n	2223.0	2223.0
		mean	29.6	319.6
		std	21.7	618.7
		median	25.0	142.7
		25th percentile	14.0	62.8
		75th percentile	41.0	346.2
		min	0.0	-39.0
		max	168.0	11250.0
	> 6 months	n	3580.0	3580.0
		mean	27.5	333.9
		std	20.0	721.9
		median	22.0	145.2
		25th percentile	14.0	66.9
		75th percentile	35.0	356.7
		min	0.0	-39.0
		max	168.0	24600.0
Cohort 3	<= 6 months	n	394.0	394.0
		mean	22.2	310.2
		std	17.7	711.6
		median	20.0	146.9

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
      be excluded after the first generic clozapine

```
                          Post-text table 3.6-1 (Continued)
           Summary statistics on duration of prodrome and slope during  prodrome for patients
                         who develped moderate leukopenia by cohort
                       (Excluded patients data meeting criteria 1, 2 and 3)
```

			Duration (day) of prodrome	Slope+
Cohort	Duration	Statistics		
Cohort 3	<= 6 months	25th percentile	8.0	67.4
		75th percentile	29.0	298.6
		min	0.0	-13.8
		max	112.0	7650.0
	6 months to 1 year	n	88.0	88.0
		mean	30.3	205.5
		std	20.4	292.7
		median	26.0	125.5
		25th percentile	14.0	62.2
		75th percentile	41.5	235.9
		min	0.0	0.0
		max	96.0	2250.0
	1-2 years	n	77.0	77.0
		mean	35.2	537.8
		std	25.1	2635.6
		median	29.0	120.7
		25th percentile	14.0	56.6
		75th percentile	46.0	259.2
		min	0.0	0.0
		max	109.0	23100.0
	> 2 years	n	49.0	49.0
		mean	36.0	307.9

```
Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
            be excluded after the first generic clozapine
```

Post-text table 3.6-1 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for patients
who develped moderate leukopenia by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 3	> 2 years	std	24.7	526.1
		median	28.0	167.4
		25th percentile	16.0	57.9
		75th percentile	42.0	363.9
		min	6.0	12.9
		max	101.0	3437.5
	> 6 months	n	214.0	214.0
		mean	33.4	348.5
		std	23.2	1611.7
		median	28.0	126.3
		25th percentile	14.0	60.8
		75th percentile	42.0	259.2
		min	0.0	0.0
		max	109.0	23100.0

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
be excluded after the first generic clozapine

```
                              Post-text table 3.6-2
    Summary statistics on duration of prodrome and slope during  prodrome for moderate leukopenia patients
                    who also developed agranulocytosis by cohort
                    (Excluded patients data meeting criteria 1, 2 and 3)
```

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 1 & 2	<= 6 months	n	334.0	334.0
		mean	26.3	320.0
		std	13.8	365.7
		median	24.0	240.8
		25th percentile	16.0	147.6
		75th percentile	35.0	372.8
		min	0.0	0.0
		max	100.0	3634.2
	6 months to 1 year	n	19.0	19.0
		mean	28.1	294.1
		std	14.6	238.5
		median	28.0	244.3
		25th percentile	16.0	138.5
		75th percentile	37.0	378.6
		min	7.0	28.2
		max	63.0	892.9
	1-2 years	n	32.0	32.0
		mean	30.9	182.8
		std	16.6	176.6
		median	28.0	150.2
		25th percentile	21.0	59.4
		75th percentile	43.5	195.0
		min	7.0	7.5

```
Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
        be excluded after the first generic clozapine
  + Slope = rate of decrease of WBC (count/day) during prodrome
```

Post-text table 3.6-2 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for moderate leukopenia patients
who also developed agranulocytosis by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 1 & 2	1-2 years	max	77.0	842.9
	> 2 years	n	48.0	48.0
		mean	29.7	404.2
		std	16.0	770.5
		median	28.0	155.6
		25th percentile	14.5	91.3
		75th percentile	42.0	363.9
		min	7.0	41.4
		max	77.0	4800.0
	> 6 months	n	99.0	99.0
		mean	29.8	311.5
		std	15.9	561.0
		median	28.0	162.6
		25th percentile	17.0	88.4
		75th percentile	42.0	335.2
		min	7.0	7.5
		max	77.0	4800.0
Cohort 3	<= 6 months	n	28.0	28.0
		mean	32.0	264.4
		std	19.2	254.8
		median	28.0	160.8

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
        be excluded after the first generic clozapine

```
                          Post-text table 3.6-2 (Continued)
    Summary statistics on duration of prodrome and slope during  prodrome for moderate leukopenia patients
                      who also developed agranulocytosis by cohort
                    (Excluded patients data meeting criteria 1, 2 and 3)
```

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 3	<= 6 months	25th percentile	15.0	129.2
		75th percentile	48.0	285.9
		min	7.0	39.9
		max	76.0	1185.7
	6 months to 1 year	n	1.0	1.0
		mean	35.0	70.7
		std	0.0	0.0
		median	35.0	70.7
		25th percentile	35.0	70.7
		75th percentile	35.0	70.7
		min	35.0	70.7
		max	35.0	70.7
	1-2 years	n	0.0	0.0
		mean	0.0	0.0
		std	0.0	0.0
		median	0.0	0.0
		25th percentile	0.0	0.0
		75th percentile	0.0	0.0
		min	0.0	0.0
		max	0.0	0.0
	> 6 months	n	1.0	1.0
		mean	35.0	70.7

```
Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
            be excluded after the first generic clozapine
```

Post-text table 3.6-2 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for moderate leukopenia patients
who also developed agranulocytosis by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 3	> 6 months	std	0.0	0.0
		median	35.0	70.7
		25th percentile	35.0	70.7
		75th percentile	35.0	70.7
		min	35.0	70.7
		max	35.0	70.7

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
            be excluded after the first generic clozapine

Post-text table 3.6-3
Summary statistics on duration of prodrome and slope during prodrome for moderate leukopenia patients
who did not developed agranulocytosis by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 1 & 2	<= 6 months	n	1444.0	1444.0
		mean	22.0	326.8
		std	15.0	1287.9
		median	21.0	149.5
		25th percentile	10.0	75.0
		75th percentile	30.0	304.0
		min	0.0	-43.6
		max	105.0	41100.0
	6 months to 1 year	n	563.0	563.0
		mean	23.2	373.7
		std	15.6	1156.8
		median	21.0	135.2
		25th percentile	13.0	75.0
		75th percentile	29.0	328.6
		min	0.0	0.0
		max	119.0	24600.0
	1-2 years	n	743.0	743.0
		mean	24.4	353.8
		std	16.7	589.6
		median	21.0	161.4
		25th percentile	14.0	74.0
		75th percentile	33.0	396.3
		min	0.0	-1.0

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
          be excluded after the first generic clozapine

```
                                 Post-text table 3.6-3 (Continued)
         Summary statistics on duration of prodrome and slope during  prodrome for moderate leukopenia patients
                          who did not developed agranulocytosis by cohort
                          (Excluded patients data meeting criteria 1, 2 and 3)


                                                             Duration (day)
         Cohort          Duration          Statistics        of prodrome           Slope+
         _____

         Cohort 1 & 2    1-2 years         max                    140.0           8766.7

                         > 2 years         n                     2175.0           2175.0
                                           mean                     29.6            317.8
                                           std                      21.8            615.0
                                           median                   24.0            141.9
                                           25th percentile          14.0             61.7
                                           75th percentile          41.0            344.7
                                           min                       0.0            -39.0
                                           max                     168.0          11250.0

                         > 6 months        n                     3481.0           3481.0
                                           mean                     27.4            334.5
                                           std                      20.1            726.0
                                           median                   22.0            144.0
                                           25th percentile          14.0             65.9
                                           75th percentile          35.0            357.1
                                           min                       0.0            -39.0
                                           max                     168.0          24600.0


         Cohort 3        <= 6 months       n                      366.0            366.0
                                           mean                     21.4            313.7
                                           std                      17.4            735.0
                                           median                   19.5            144.1
         _____
```

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
        be excluded after the first generic clozapine
  + Slope = rate of decrease of WBC (count/day) during prodrome

Post-text table 3.6-3 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for moderate leukopenia patients
who did not developed agranulocytosis by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 3	<= 6 months	25th percentile	7.0	66.7
		75th percentile	28.0	298.6
		min	0.0	-13.8
		max	112.0	7650.0
	6 months to 1 year	n	87.0	87.0
		mean	30.3	207.1
		std	20.5	294.0
		median	25.0	125.9
		25th percentile	14.0	61.7
		75th percentile	42.0	236.0
		min	0.0	0.0
		max	96.0	2250.0
	1-2 years	n	77.0	77.0
		mean	35.2	537.8
		std	25.1	2635.6
		median	29.0	120.7
		25th percentile	14.0	56.6
		75th percentile	46.0	259.2
		min	0.0	0.0
		max	109.0	23100.0
	> 2 years	n	49.0	49.0
		mean	36.0	307.9

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
          be excluded after the first generic clozapine

Post-text table 3.6-3 (Continued)
Summary statistics on duration of prodrome and slope during prodrome for moderate leukopenia patients
who did not developed agranulocytosis by cohort
(Excluded patients data meeting criteria 1, 2 and 3)

Cohort	Duration	Statistics	Duration (day) of prodrome	Slope+
Cohort 3	> 2 years	std	24.7	526.1
		median	28.0	167.4
		25th percentile	16.0	57.9
		75th percentile	42.0	363.9
		min	6.0	12.9
		max	101.0	3437.5
	> 6 months	n	213.0	213.0
		mean	33.4	349.8
		std	23.3	1615.4
		median	28.0	126.5
		25th percentile	14.0	60.8
		75th percentile	42.0	259.2
		min	0.0	0.0
		max	109.0	23100.0

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
           be excluded after the first generic clozapine

Post-text table 3.6-4
Number of agranulocytosis and severe leukopenia cases projected to occur after change from bi-weekly monitoring for
Cohort 3
(Excluded patients' data meeting criteria 1, 2 and 3)

	Change monitoring after	No. of cases			Patient Year	Rate per 1000 patient-years		
		Bi-weekly (actual)	Monthly	No Monitoring		Bi-weekly (actual)	Monthly	No Monitoring
Agran	Six months	7*	45	157	27017	0.26	1.68	5.81
	One year	2	28	88	17595	0.11	1.57	4.98
	Two years	0	9	34	6030	0.00	1.51	5.66
Severe Leukopenia	Six months	9	100	230	27017	0.33	3.68	8.51
	One year	5	61	128	17595	0.28	3.46	7.27
	Two years	4	20	50	6030	0.66	3.29	8.29

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
             be excluded after the first generic clozapine

* Excluded 3 patients with less than 6 months of treatment but the reporting date of
  agranulocytosis was more than 6 months from start of therapy.

Post-text table 3.6-5
cumulative number* of agranulocytosis and severe leukopenia cases projected to occur beginning 6 months
after initiation of Clozaril therapy, by timing of reduction in frequency of WBC monitoring for Cohort 3
(Excluded patients' data meeting criteria 1, 2 and 3)

| | Change monitoring after | No. of cases | | | Patient Year | Rate per 1000 patient-years | | |
		Bi-weekly (actual)	Monthly	No Monitoring		Bi-weekly (actual)	Monthly	No Monitoring
Agran	Six months	7#	45	157	27017	0.26	1.68	5.81
	One year	7#	33	93	27017	0.26	1.21	3.43
	Two years	7#	16	41	27017	0.26	0.60	1.52
Severe Leukopenia	Six months	9	100	230	27017	0.33	3.68	8.51
	One year	9	65	132	27017	0.33	2.40	4.89
	Two years	9	25	55	27017	0.33	0.92	2.04

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
be excluded after the first generic clozapine

* Actual number of cases occurred after 6 months of treatment and before change monitoring were added to
the projected number of cases so that cumulative number of cases were comparable under different monitoring
systems.
Excluded 3 patients with less than 6 months of treatment but the reporting date of
agranulocytosis was more than 6 months from start of therapy.

Post-text table 3.6-6
Additional cases of agranulocytosis and severe leukopenia projected to occur after 6 months as a result of switching from bi-weekly to less-frequent WBC monitoring for Cohort 3
(Excluded patients' data meeting criteria 1, 2 and 3)

| | Change Monitoring after | No. of cases | | | Rate per 1000 patient-years | |
		Monthly	No Monitoring	Patient Year	Monthly	No Monitoring
Agran	Six months	38	150	27017	1.42	5.55
	One year	26	86	27017	0.95	3.17
	Two years	9	34	27017	0.34	1.26
Severe Leukopenia	Six months	91	221	27017	3.35	8.18
	One year	56	123	27017	2.07	4.55
	Two years	16	46	27017	0.59	1.70

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before Clozaril
Criteria 3: Patients started on Clozaril, but switched to generic after Dec. 1, 97. All data will
           be excluded after the first generic clozapine

Post-text table 3.6-7: Projection of Total Number of Deaths for Different Monitoring Systems

The estimated proportions of deaths due to agranulocytosis for cohort 3 are:

　　3.55% for Clozaril treated Cohort 3 patients under the current bi-weekly monitoring.
　　15% under no monitoring or other causes of agranulocytosis.

Assuming these death rates, the following table shows the estimated total
number of deaths due to agranulocytosis that would have occurred between
10/1/97 and 9/1/01 if monitoring was changed.

(N=39,260) (Person Year=41,172) Death Rate Due to Agranulocytosis	At Six Months of Therapy		At One Year of Therapy		At Two Years of Therapy	
	Monthly (Projected)	No Monitoring (Projected)	Monthly (Projected)	No Monitoring (Projected)	Monthly (Projected)	No Monitoring (Projected)
3.55%	4 *1**	8 *5*	4 *1*	6 *3*	3 *0*	4 *1*
15%	9 *6*	25 *22*	7 *4*	16 *13*	4 *1*	8 *5*

* *italic* = estimated additional cases (additional cases of agranulocytosis multiplied by the death rate)

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