

Clozaril® (clozapine) Tablets

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

Appendix 2: Post-text Tables (United Kingdom Data)

Document status: Final

Release date: May 19, 2003

Number of pages: 44

Available for public disclosure without redaction

Table of contents

1	Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.....	4
2	Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.....	5
3	Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.....	6
4	Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.....	7
5	Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.....	9
6	Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.....	10
7	Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.....	11
8	Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.....	12
9	Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.....	13
10	Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.....	14
11	Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.....	16
12	Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.....	17
13	Red Alert incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.....	18
14	Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (3 periods), in the UK CPMS.....	19
15	Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.....	21
16	Red alert incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.....	25
17	Red alert incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.....	26
18	Red alert incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.....	28
19	Red alert incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.....	29
20	Red alert treatment withdrawal criteria, in the UK CPMS.....	31

21 Demographic characteristics of the UK CPMS patients included in the analysis, by cohort.....	32
22 Demographic characteristics of the UK CPMS patients with agranulocytosis , by cohort.....	33
23 Demographic characteristics of the UK CPMS patients with severe leukopenia, by cohort.....	34
24 Demographic characteristics of the UK CPMS patients with red alert, by cohort.....	35
Figures	36
1) Agranulocytosis incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).	37
2) Agranulocytosis incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).....	38
3) Severe leukopenia incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).	39
4) Severe leukopenia incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).	40
5) Red alert incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).....	41
6) Red alert incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).....	42

1 Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

Table 4.1. Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

	Cases	Pat-yrs	Incidence	95%	CI
Trt duration					
0-18 wks	162	7,579.46	21.37	18.08	24.66
19-52 wks	16	11,147.43	1.44	0.82	2.33
+52 wks	40	56,757.91	0.70	0.49	0.92

2 Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.**Table 4.2. Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.**

		Cases	Pat-yrs	Incidence	95%	CI
trt duration	Calendar year					
0-18 wks	1990	4	131.03	30.53	8.32	78.15
	1991	7	394.33	17.75	7.14	36.57
	1992	11	415.40	26.48	13.22	47.38
	1993	11	421.84	26.08	13.02	46.65
	1994	15	430.83	34.82	19.49	57.42
	1995	13	592.05	21.96	11.69	37.55
	1996	18	765.97	23.50	13.93	37.14
	1997	4	574.28	6.97	1.90	17.83
	1998	19	765.86	24.81	14.94	38.74
	1999	29	945.67	30.67	19.50	41.83
	2000	19	969.67	19.59	11.80	30.60
	2001	12	1,010.03	11.88	6.14	20.75
	2002	.	162.50	.	.	.
19-52 wks	1990	.	56.70	.	.	.
	1991	1	374.28	2.67	0.07	14.89
	1992	.	630.79	.	.	.
	1993	2	662.72	3.02	0.37	10.90
	1994	.	585.94	.	.	.
	1995	1	797.02	1.25	0.03	6.99
	1996	2	1,159.13	1.73	0.21	6.23
	1997	2	994.78	2.01	0.24	7.26
	1998	3	1,037.32	2.89	0.60	8.45
	1999	2	1,430.98	1.40	0.17	5.05
	2000	2	1,499.66	1.33	0.16	4.82
	2001	1	1,645.98	0.61	0.02	3.39
	2002	.	272.15	.	.	.

Table 4.2. Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1990	.	1.69	.	.	.
	1991	.	141.41	.	.	.
	1992	1	747.61	1.34	0.03	7.45
	1993	.	1,572.48	.	.	.
	1994	1	2,302.91	0.43	0.01	2.42
	1995	1	3,009.96	0.33	0.01	1.85
	1996	3	4,232.59	0.71	0.15	2.07
	1997	4	5,535.94	0.72	0.20	1.85
	1998	4	6,718.51	0.60	0.16	1.52
	1999	9	8,129.39	1.11	0.51	2.10
	2000	10	10,091.22	0.99	0.48	1.82
	2001	7	12,077.15	0.58	0.23	1.19
	2002	.	2,197.04	.	.	.

3 Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.

Table 4.3. Agranulocytosis incidence per 1,000 person-years and 95% CI by treatment duration and monitoring frequency, in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
trt duration	Monitoring freq.					
	0-18 wks	1W	162	7,575.17	21.39	18.09
	19-52 wks	1W	12	2,506.63	4.79	2.47
+52 wks		2W	4	8,616.53	0.46	0.13
		1W	17	2,518.03	6.75	3.93
		2W	6	10,978.36	0.55	0.20
		4W	17	43,181.76	0.39	0.23
						0.63

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

4 Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

Table 4.4. Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

trt duration	monitor	Calendar year	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1W	1990-1991	11	524.90	20.96	10.46	37.49
		1992-1993	22	836.64	26.30	15.31	37.28
		1994-1995	28	1,022.03	27.40	17.25	37.54
		1996-1997	22	1,339.29	16.43	9.56	23.29
		1998-1999	48	1,710.74	28.06	20.12	36.00
		2000-2002*	31	2,141.58	14.48	9.38	19.57
19-52 wks	1W	1990-1991	1	115.98	8.62	0.22	48.04
		1992-1993	2	295.12	6.78	0.82	24.48
		1994-1995	1	315.53	3.17	0.08	17.66
		1996-1997	3	472.24	6.35	1.31	18.56
		1998-1999	3	577.84	5.19	1.07	15.17
		2000-2002*	2	729.92	2.74	0.33	9.90
	2W	1990-1991	.	314.03	.	.	.
		1992-1993	.	995.66	.	.	.
		1994-1995	.	1,064.82	.	.	.
		1996-1997	1	1,677.30	0.60	0.01	3.32
		1998-1999	2	1,884.78	1.06	0.13	3.83
		2000-2002*	1	2,679.93	0.37	0.01	2.08

Table 4.4. Agranulocytosis incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	1990-1991	.	13.73	.	.	.
		1992-1993	.	207.76	.	.	.
		1994-1995	2	346.71	5.77	0.70	20.84
		1996-1997	1	434.40	2.30	0.06	12.83
		1998-1999	6	646.84	9.28	3.40	20.19
		2000-2002*	8	868.59	9.21	3.98	18.14
	2W	1990-1991	.	128.91	.	.	.
		1992-1993	1	2,107.50	0.47	0.01	2.64
		1994-1995	.	3,828.73	.	.	.
		1996-1997	2	1,524.43	1.31	0.16	4.74
		1998-1999	1	1,594.00	0.63	0.02	3.50
		2000-2002*	2	1,794.79	1.11	0.13	4.03
	4W	1994-1995	.	1,128.30	.	.	.
		1996-1997	4	7,795.15	0.51	0.14	1.31
		1998-1999	6	12,586.90	0.48	0.17	1.04
		2000-2002*	7	21,671.41	0.32	0.13	0.67

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

5 Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

Table 4.5. Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
Trt duration	Cohort					
0-18 wks	Initial system	43	1,731.75	24.83	17.41	32.25
	Current system, new patients	119	5,839.83	20.38	16.72	24.04
	Current system, old patients	.	1.20	.	.	.
19-52 wks	Initial system	3	2,586.62	1.16	0.24	3.39
	Current system, new patients	13	8,552.11	1.52	0.81	2.60
	Current system, old patients	.	3.14	.	.	.
+52 wks	Initial system	2	6,542.55	0.31	0.04	1.10
	Current system, new patients	18	30,693.75	0.59	0.35	0.93
	Current system, old patients	20	19,499.30	1.03	0.63	1.58

6 Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

Table 4.6. Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort style, in the US CPMS.

Trt duration	monitor	Cohort	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1W	Initial system	43	1,730.38	24.85	17.42	32.28
		Current system, new patients	119	5,836.92	20.39	16.72	24.05
		Current system, old patients	.	1.20	.	.	.
19-52 wks	1W	Initial system	3	576.70	5.20	1.07	15.20
		Current system, new patients	9	1,927.84	4.67	2.13	8.86
		Current system, old patients	.	0.79	.	.	.
	2W	Initial system	.	2,004.42	.	.	.
		Current system, new patients	4	6,605.80	0.61	0.17	1.55
		Current system, old patients	.	2.05	.	.	.

Table 4.6. Agranulocytosis incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort style, in the US CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	Initial system	1	492.97	2.03	0.05	11.30
		Current system, new patients	6	1,303.73	4.60	1.69	10.02
		Current system, old patients	10	718.72	13.91	6.67	25.59
	2W	Initial system	1	6,038.57	0.17	0.00	0.92
		Current system, new patients	3	3,310.65	0.91	0.19	2.65
		Current system, old patients	2	1,625.35	1.23	0.15	4.45
	4W	Current system, new patients	9	26,034.87	0.35	0.16	0.66
		Current system, old patients	8	17,131.16	0.47	0.20	0.92

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

7 Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

Table 4.7. Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

	Cases	Pat-yrs	Incidence	95%	CI
trt duration					
0-18 wks	244	7,579.46	32.19	28.15	36.23
19-52 wks	45	11,147.43	4.04	2.86	5.22
+52 wks	111	56,757.91	1.96	1.59	2.32

8 Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.**Table 4.8. Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.**

Trt duration	Calendar year	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1990	7	131.03	53.42	21.48	110.05
	1991	12	394.33	30.43	15.73	53.15
	1992	14	415.40	33.70	18.43	56.55
	1993	13	421.84	30.82	16.41	52.70
	1994	18	430.83	41.78	24.77	66.03
	1995	18	592.05	30.40	18.02	48.05
	1996	22	765.97	28.72	16.72	40.72
	1997	15	574.28	26.12	14.62	43.08
	1998	27	765.86	35.25	21.96	48.55
	1999	44	945.67	46.53	32.78	60.28
	2000	26	969.67	26.81	16.51	37.12
	2001	22	1,010.03	21.78	12.68	30.88
	2002	6	162.50	36.92	13.55	80.37
19-52 wks	1990	.	56.70	.	.	.
	1991	2	374.28	5.34	0.65	19.30
	1992	3	630.79	4.76	0.98	13.90
	1993	4	662.72	6.04	1.64	15.45
	1994	1	585.94	1.71	0.04	9.51
	1995	3	797.02	3.76	0.78	11.00
	1996	4	1,159.13	3.45	0.94	8.83
	1997	5	994.78	5.03	1.63	11.73
	1998	6	1,037.32	5.78	2.12	12.59
	1999	5	1,430.98	3.49	1.13	8.16
	2000	7	1,499.66	4.67	1.88	9.62
	2001	4	1,645.98	2.43	0.66	6.22
	2002	1	272.15	3.67	0.09	20.47

Table 4.8. Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration, in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1990	.	1.69	.	.	.
	1991	1	141.41	7.07	0.18	39.40
	1992	3	747.61	4.01	0.83	11.73
	1993	4	1,572.48	2.54	0.69	6.51
	1994	5	2,302.91	2.17	0.70	5.07
	1995	3	3,009.96	1.00	0.21	2.91
	1996	8	4,232.59	1.89	0.82	3.72
	1997	8	5,535.94	1.45	0.62	2.85
	1998	14	6,718.51	2.08	1.14	3.50
	1999	19	8,129.39	2.34	1.41	3.65
	2000	27	10,091.22	2.68	1.67	3.68
	2001	17	12,077.15	1.41	0.82	2.25
	2002	2	2,197.04	0.91	0.11	3.29

9 Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.

Table 4.9. Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
Trt duration	Monitor					
0-18 wks	1W	244	7,575.17	32.21	28.17	36.25
	2W					
19-52 wks	1W	39	2,506.63	15.56	10.68	20.44
	2W					
	4W	72	2,518.03	28.59	21.99	35.20
+52 wks	1W	13	10,978.36	1.18	0.63	2.02
	2W					
	4W	25	43,181.76	0.58	0.35	0.81

10 Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.**Table 4.10. Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.**

trt duration	monitor	Calendar year	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1W	1990-1991	19	524.90	36.20	21.79	56.53
		1992-1993	27	836.64	32.27	20.10	44.44
		1994-1995	36	1,022.03	35.22	23.72	46.73
		1996-1997	37	1,339.29	27.63	18.72	36.53
		1998-1999	71	1,710.74	41.50	31.85	51.16
	1W	2000-2002*	54	2,141.58	25.22	18.49	31.94
		1990-1991	1	115.98	8.62	0.22	48.04
		1992-1993	7	295.12	23.72	9.54	48.86
		1994-1995	4	315.53	12.68	3.45	32.45
		1996-1997	7	472.24	14.82	5.96	30.54
19-52 wks	1W	1998-1999	10	577.84	17.31	8.30	31.83
		2000-2002*	10	729.92	13.70	6.57	25.19
	2W	1990-1991	1	314.03	3.18	0.08	17.74
		1992-1993	.	995.66	.	.	.
		1994-1995	.	1,064.82	.	.	.
		1996-1997	2	1,677.30	1.19	0.14	4.31
		1998-1999	1	1,884.78	0.53	0.01	2.96
		2000-2002*	2	2,679.93	0.75	0.09	2.70

Table 4.10. Severe leukopenia incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	1990-1991	1	13.73	72.83	1.82	405.82
		1992-1993	4	207.76	19.25	5.25	49.29
		1994-1995	4	346.71	11.54	3.14	29.53
		1996-1997	11	434.40	25.32	12.64	45.30
		1998-1999	24	646.84	37.10	22.26	51.95
		2000-2002*	28	868.59	32.24	20.30	44.18
	2W	1990-1991	.	128.91	.	.	.
		1992-1993	3	2,107.50	1.42	0.29	4.16
		1994-1995	4	3,828.73	1.04	0.28	2.67
		1996-1997	1	1,524.43	0.66	0.02	3.66
		1998-1999	2	1,594.00	1.25	0.15	4.53
		2000-2002*	3	1,794.79	1.67	0.34	4.88
	4W	1994-1995	.	1,128.30	.	.	.
		1996-1997	4	7,795.15	0.51	0.14	1.31
		1998-1999	7	12,586.90	0.56	0.22	1.15
		2000-2002*	14	21,671.41	0.65	0.35	1.08

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

11 Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

Table 4.11. Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
trt duration	Cohort					
0-18 wks	Initial system	58	1,731.75	33.49	24.87	42.11
	Current system, new patients	186	5,839.83	31.85	27.27	36.43
	Current system, old patients	.	1.20	.	.	.
19-52 wks	Initial system	11	2,586.62	4.25	2.12	7.61
	Current system, new patients	34	8,552.11	3.98	2.64	5.31
	Current system, old patients	.	3.14	.	.	.
+52 wks	Initial system	17	6,542.55	2.60	1.51	4.16
	Current system, new patients	58	30,693.75	1.89	1.40	2.38
	Current system, old patients	34	19,499.30	1.74	1.16	2.33

12 Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

Table 4.12. Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

Trt duration	monitor	Cohort	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1W	Initial system	58	1,730.38	33.52	24.89	42.15
		Current system, new patients	186	5,836.92	31.87	27.29	36.45
		Current system, old patients	.	1.20	.	.	.
19-52 wks	1W	Initial system	10	576.70	17.34	8.31	31.89
		Current system, new patients	29	1,927.84	15.04	9.57	20.52
		Current system, old patients	.	0.79	.	.	.
	2W	Initial system	1	2,004.42	0.50	0.01	2.78
		Current system, new patients	5	6,605.80	0.76	0.25	1.77
		Current system, old patients	.	2.05	.	.	.

Table 4.12. Severe leukopenia incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	Initial system	10	492.97	20.29	9.73	37.30
		Current system, new patients	38	1,303.73	29.15	19.88	38.41
		Current system, old patients	22	718.72	30.61	17.82	43.40
	2W	Initial system	7	6,038.57	1.16	0.47	2.39
		Current system, new patients	4	3,310.65	1.21	0.33	3.09
		Current system, old patients	2	1,625.35	1.23	0.15	4.45
4W	2W	Current system, new patients	16	26,034.87	0.61	0.35	1.00
		Current system, old patients	9	17,131.16	0.53	0.24	1.00

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

13 Red Alert incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

Table 4.13. Red alert incidence per 1,000 person-years and 95% CI, by treatment duration, in the UK CPMS.

	Cases	Pat-yrs	Incidence	95%	CI
trt duration					
0-18 wks	664	7,579.46	87.61	80.94	94.27
19-52 wks	256	11,147.43	22.96	20.15	25.78
+52 wks	421	56,757.91	7.42	6.71	8.13

14 Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (3 periods), in the UK CPMS.**Table 4.14. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (3 periods), in the UK CPMS.**

Trt duration	Calendar year	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1990	17	131.03	129.74	75.58	207.74
	1991	44	394.33	111.58	78.61	144.55
	1992	42	415.40	101.11	70.53	131.68
	1993	46	421.84	109.05	77.53	140.56
	1994	47	430.83	109.09	77.90	140.28
	1995	54	592.05	91.21	66.88	115.54
	1996	61	765.97	79.64	59.65	99.62
	1997	40	574.28	69.65	48.07	91.24
	1998	73	765.86	95.32	73.45	117.18
	1999	88	945.67	93.06	73.61	112.50
	2000	75	969.67	77.35	59.84	94.85
	2001	64	1,010.03	63.36	47.84	78.89
19-52 wks	2002	12	162.50	73.85	38.16	128.98
	1990	2	56.70	35.27	4.27	127.43
	1991	14	374.28	37.41	20.45	62.76
	1992	18	630.79	28.54	16.92	45.10
	1993	29	662.72	43.76	27.83	59.69
	1994	8	585.94	13.65	5.89	26.90
	1995	19	797.02	23.84	14.35	37.23
	1996	23	1,159.13	19.84	11.73	27.95
	1997	18	994.78	18.09	10.73	28.60
	1998	31	1,037.32	29.88	19.36	40.41
	1999	31	1,430.98	21.66	14.04	29.29
	2000	25	1,499.66	16.67	10.14	23.21
	2001	34	1,645.98	20.66	13.71	27.60
	2002	4	272.15	14.70	4.01	37.63

Table 4.14. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (3 periods), in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1990	.	1.69	.	.	.
	1991	2	141.41	14.14	1.71	51.09
	1992	11	747.61	14.71	7.34	26.32
	1993	22	1,572.48	13.99	8.14	19.84
	1994	24	2,302.91	10.42	6.25	14.59
	1995	25	3,009.96	8.31	5.05	11.56
	1996	27	4,232.59	6.38	3.97	8.79
	1997	37	5,535.94	6.68	4.53	8.84
	1998	38	6,718.51	5.66	3.86	7.45
	1999	63	8,129.39	7.75	5.84	9.66
	2000	74	10,091.22	7.33	5.66	9.00
	2001	84	12,077.15	6.96	5.47	8.44
	2002	14	2,197.04	6.37	3.48	10.69

15 Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.**Table 4.15. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.**

		Cases	Pat-yrs	Incidence	95%	CI
Trt duration	Calendar year					
0-6 months	1990	18	156.61	114.94	68.13	181.66
	1991	49	515.49	95.05	68.44	121.67
	1992	46	572.54	80.34	57.13	103.56
	1993	56	586.39	95.50	70.49	120.51
	1994	50	583.93	85.63	61.89	109.36
	1995	64	803.47	79.65	60.14	99.17
	1996	71	1,066.48	66.57	51.09	82.06
	1997	50	797.96	62.66	45.29	80.03
	1998	84	1,037.57	80.96	63.65	98.27
	1999	102	1,307.23	78.03	62.88	93.17
	2000	83	1,332.41	62.29	48.89	75.69
	2001	76	1,408.42	53.96	41.83	66.09
6-12 months	2002	14	225.69	62.03	33.91	104.08
	1990	1	31.12	32.14	0.80	179.06
	1991	9	253.12	35.56	16.26	67.52
	1992	14	473.65	29.56	16.16	49.59
	1993	19	498.17	38.14	22.96	59.56
	1994	5	432.85	11.55	3.75	26.96
	1995	9	585.60	15.37	7.03	29.18
	1996	13	858.63	15.14	8.06	25.89
	1997	8	771.10	10.37	4.48	20.44
	1998	20	765.61	26.12	15.96	40.35
	1999	17	1,069.42	15.90	9.26	25.45
	2000	17	1,136.91	14.95	8.71	23.94
	2001	22	1,247.58	17.63	10.27	25.00
	2002	2	208.96	9.57	1.16	34.58

Table 4.15. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
1-2 yrs	1990	.	1.69	.	.	.
	1991	2	139.85	14.30	1.73	51.66
	1992	10	615.56	16.25	7.79	29.88
	1993	11	880.96	12.49	6.23	22.34
	1994	12	865.40	13.87	7.17	24.22
	1995	4	844.15	4.74	1.29	12.13
	1996	9	1,201.30	7.49	3.43	14.23
	1997	13	1,551.52	8.38	4.46	14.33
	1998	9	1,343.70	6.70	3.06	12.72
	1999	12	1,536.78	7.81	4.04	13.64
	2000	20	2,069.81	9.66	5.90	14.92
	2001	20	2,137.51	9.36	5.72	14.45
	2002	2	385.31	5.19	0.63	18.75
2-3 yrs	1991	.	1.56	.	.	.
	1992	1	130.91	7.64	0.19	42.56
	1993	9	567.66	15.85	7.25	30.11
	1994	9	784.19	11.48	5.25	21.79
	1995	9	785.30	11.46	5.24	21.76
	1996	5	830.19	6.02	1.95	14.06
	1997	5	1,085.79	4.60	1.49	10.75
	1998	10	1,480.25	6.76	3.24	12.42
	1999	13	1,306.44	9.95	5.30	17.02
	2000	5	1,498.00	3.34	1.08	7.79
	2001	18	2,000.27	9.00	5.33	14.22
	2002	4	328.92	12.16	3.31	31.13

Table 4.15. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
3-4 yrs	1992	.	1.14	.	.	.
	1993	2	122.71	16.30	1.97	58.88
	1994	3	532.89	5.63	1.16	16.45
	1995	7	750.70	9.32	3.75	19.21
	1996	2	791.33	2.53	0.31	9.13
	1997	4	785.56	5.09	1.39	13.04
	1998	5	1,050.66	4.76	1.54	11.11
	1999	11	1,433.33	7.67	3.83	13.73
	2000	11	1,277.78	8.61	4.30	15.40
	2001	10	1,459.22	6.85	3.29	12.60
	2002	2	296.60	6.74	0.82	24.36
4-5 yrs	1992
	1993	.	1.15	.	.	.
	1994	.	119.33	.	.	.
	1995	5	512.37	9.76	3.17	22.78
	1996	8	760.57	10.52	4.54	20.72
	1997	7	758.19	9.23	3.71	19.02
	1998	8	767.03	10.43	4.50	20.55
	1999	9	1,023.35	8.79	4.02	16.70
	2000	16	1,412.07	11.33	6.48	18.40
	2001	10	1,259.16	7.94	3.81	14.60
	2002	2	208.53	9.59	1.16	34.65
5-6 yrs	1994	.	1.09	.	.	.
	1995	.	116.32	.	.	.
	1996	1	526.84	1.90	0.05	10.58
	1997	4	724.06	5.52	1.51	14.14
	1998	5	737.86	6.78	2.20	15.82
	1999	6	759.48	7.90	2.90	17.20
	2000	5	1,012.04	4.94	1.60	11.53
	2001	9	1,397.41	6.44	2.94	12.23
	2002	2	226.66	8.82	1.07	31.88

Table 4.15. Red alert incidence per 1,000 person-years and 95% CI, by calendar year and treatment duration (12 periods), in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
6-7 yrs	1995	.	1.13	.	.	.
	1996	2	121.12	16.51	2.00	59.65
	1997	2	509.52	3.93	0.47	14.18
	1998	1	713.63	1.40	0.04	7.81
	1999	6	732.03	8.20	3.01	17.84
	2000	4	753.58	5.31	1.45	13.59
	2001	7	1,007.17	6.95	2.79	14.32
	2002	1	204.06	4.90	0.12	27.31
7-8 yrs	1996	.	1.22	.	.	.
	1997	2	120.02	16.66	2.02	60.20
	1998	.	506.01	.	.	.
	1999	3	706.52	4.25	0.88	12.41
	2000	4	733.75	5.45	1.49	13.96
	2001	2	747.44	2.68	0.32	9.67
	2002	.	147.97	.	.	.
	1997	.	1.28	.	.	.
8-9 yrs	1998	.	118.35	.	.	.
	1999	3	512.29	5.86	1.21	17.11
	2000	6	705.50	8.50	3.12	18.51
	2001	3	734.61	4.08	0.84	11.93
	2002	.	111.43	.	.	.
	1998	.	1.03	.	.	.
	1999	.	118.15	.	.	.
	2000	2	508.27	3.93	0.48	14.21
>10 yrs	2001	2	707.49	2.83	0.34	10.21
	2002	.	115.89	.	.	.
	1999	.	1.03	.	.	.
	2000	1	120.42	8.30	0.21	46.27
	2001	3	626.86	4.79	0.99	13.99
	2002	1	171.69	5.82	0.15	32.45

16 Red alert incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.

Table 4.16. Red alert incidence per 1,000 person-years and 95% CI, by treatment duration and monitoring frequency, in the UK CPMS.

		Cases	Pat-yrs	Incidence	95%	CI
Trt duration	Monitor					
0-18 wks	1W	658	7,575.17	86.86	80.23	93.50
	19-52 wks	1W	223	2,506.63	88.96	77.29
		2W	33	8,616.53	3.83	2.52
+52 wks	1W	309	2,518.03	122.71	109.03	136.40
	2W	40	10,978.36	3.64	2.51	4.77
		4W	71	43,181.76	1.64	1.26

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

17 Red alert incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

Table 4.17. Red alert incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

Trt duration	monitor	Calendar year	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	1W	1990-1991	61	524.90	116.21	87.05	145.38
		1992-1993	88	836.64	105.18	83.21	127.16
		1994-1995	100	1,022.03	97.84	78.67	117.02
		1996-1997	98	1,339.29	73.17	58.69	87.66
		1998-1999	161	1,710.74	94.11	79.57	108.65
	1W	2000-2002*	150	2,141.58	70.04	58.83	81.25
		1990-1991	13	115.98	112.09	59.68	191.67
		1992-1993	43	295.12	145.70	102.15	189.25
		1994-1995	26	315.53	82.40	50.73	114.07
		1996-1997	33	472.24	69.88	46.04	93.72
19-52 wks	1W	1998-1999	54	577.84	93.45	68.53	118.38
		2000-2002*	54	729.92	73.98	54.25	93.71
	2W	1990-1991	3	314.03	9.55	1.97	27.92
		1992-1993	4	995.66	4.02	1.09	10.28
		1994-1995	1	1,064.82	0.94	0.02	5.23
		1996-1997	8	1,677.30	4.77	2.06	9.40
		1998-1999	8	1,884.78	4.24	1.83	8.36
	2W	2000-2002*	9	2,679.93	3.36	1.54	6.38

Table 4.17. Red alert incidence per 1,000 person-years and 95% CI, by calendar year (2-year intervals), treatment duration and monitoring frequency, in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	1990-1991	1	13.73	72.83	1.82	405.82
		1992-1993	27	207.76	129.96	80.94	178.98
		1994-1995	34	346.71	98.06	65.10	131.03
		1996-1997	51	434.40	117.40	85.18	149.63
		1998-1999	73	646.84	112.86	86.97	138.75
		2000-2002*	123	868.59	141.61	116.58	166.63
	2W	1990-1991	1	128.91	7.76	0.19	43.22
		1992-1993	6	2,107.50	2.85	1.04	6.20
		1994-1995	14	3,828.73	3.66	2.00	6.14
		1996-1997	4	1,524.43	2.62	0.72	6.72
		1998-1999	6	1,594.00	3.76	1.38	8.19
		2000-2002*	9	1,794.79	5.01	2.29	9.52
	4W	1994-1995	1	1,128.30	0.89	0.02	4.94
		1996-1997	9	7,795.15	1.15	0.53	2.19
		1998-1999	22	12,586.90	1.75	1.02	2.48
		2000-2002*	39	21,671.41	1.80	1.23	2.36

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

18 Red alert incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

Table 4.18. Red incidence per 1,000 person-years and 95% CI, by treatment duration and cohort in the UK CPMS.

Trt duration	Cohort	Cases	Pat-yrs	Incidence	95%	CI
0-18 wks	Initial system	182	1,731.75	105.10	89.83	120.36
	Current system, new patients	482	5,839.83	82.54	75.17	89.91
	Current system, old patients	.	1.20	.	.	.
19-52 wks	Initial system	79	2,586.62	30.54	23.81	37.28
	Current system, new patients	177	8,552.11	20.70	17.65	23.75
	Current system, old patients	.	3.14	.	.	.
+52 wks	Initial system	77	6,542.55	11.77	9.14	14.40
	Current system, new patients	228	30,693.75	7.43	6.46	8.39
	Current system, old patients	113	19,499.30	5.80	4.73	6.86

19 Red alert incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

Table 4.19. Red incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
Trt duration	monitor	Cohort					
0-18 wks	1W	Initial system	180	1,730.38	104.02	88.83	119.22
		Current system, new patients	478	5,836.92	81.89	74.55	89.23
		Current system, old patients	.	1.20	.	.	.
	1W	Initial system	72	576.70	124.85	96.01	153.69
		Current system, new patients	151	1,927.84	78.33	65.83	90.82
		Current system, old patients	.	0.79	.	.	.
	2W	Initial system	7	2,004.42	3.49	1.40	7.19
		Current system, new patients	26	6,605.80	3.94	2.42	5.45
		Current system, old patients	.	2.05	.	.	.

Table 4.19. Red incidence per 1,000 person-years and 95% CI, by treatment duration, monitoring frequency and cohort in the UK CPMS.

			Cases	Pat-yrs	Incidence	95%	CI
+52 wks	1W	Initial system	57	492.97	115.62	85.61	145.64
		Current system, new patients	170	1,303.73	130.39	110.79	150.00
		Current system, old patients	80	718.72	111.31	86.92	135.70
	2W	Initial system	20	6,038.57	3.31	2.02	5.12
		Current system, new patients	14	3,310.65	4.23	2.31	7.10
		Current system, old patients	6	1,625.35	3.69	1.35	8.04
	4W	Current system, new patients	44	26,034.87	1.69	1.19	2.19
		Current system, old patients	26	17,131.16	1.52	0.93	2.10

1W - patients who were monitored weekly

2W - patients who were monitored every two weeks

4W - patients who were monitored every four weeks (monthly)

20 Red alert treatment withdrawal criteria, in the UK CPMS

Table 4.20. Red alert treatment withdrawal criteria, in the UK CPMS.

Criteria	n	%
Agran	215	16.03
Neutropenia	762	56.82
Other	215	16.03
Leucopenia	149	11.11

21 Demographic characteristics of the UK CPMS patients included in the analysis, by cohort.

Table 4.21. Demographic characteristics of the UK CPMS patients included in the analysis, by cohort.

	All	Cohort							
				Initial system		Current system, new patients			
		n	%	n	%	n	%	n	%
Sex									
F	9077	32.54	13	28.26	2174	34.10	6890	32.09	
M	18817	67.46	33	71.74	4201	65.90	14583	67.91	
Age groups									
<=35	14483	51.92	27	58.70	3220	50.51	11236	52.33	
36-50	9273	33.24	12	26.09	2208	34.64	7053	32.85	
51-65	3400	12.19	6	13.04	767	12.03	2627	12.23	
>65	738	2.65	1	2.17	180	2.82	557	2.59	
Race									
AFRO-CARIB	1669	5.98	2	4.35	278	4.36	1389	6.47	
ASIAN	1206	4.32	3	6.52	206	3.23	997	4.64	
CAUCASIAN	24444	87.63	37	80.43	5755	90.27	18652	86.86	
MIXED	460	1.65	3	6.52	112	1.76	345	1.61	
ORIENTAL	115	0.41	1	2.17	24	0.38	90	0.42	

22 Demographic characteristics of the UK CPMS patients with agranulocytosis , by cohort.

Table 4.22. Demographic characteristics of the UK CPMS patients with agranulocytosis , by cohort.

	All	Cohort					
		Initial system		Current system, new patients		Current system, old patients	
		n	%	n	%	n	%
Sex							
F	85	38.99		20	41.67	58	38.67
M	133	61.01		28	58.33	92	61.33
Age groups							
<=35	52	23.85		12	25.00	35	23.33
36-50	91	41.74		25	52.08	54	36.00
51-65	66	30.28		11	22.92	52	34.67
>65	9	4.13		.	.	9	6.00
Race							
AFRO-CARIB	3	1.38		1	2.08	1	0.67
ASIAN	11	5.05		2	4.17	9	6.00
CAUCASIAN	202	92.66		45	93.75	138	92.00
MIXED	2	0.92		.	.	2	1.33

23 Demographic characteristics of the UK CPMS patients with severe leukopenia, by cohort.

Table 4.23. Demographic characteristics of the UK CPMS patients with severe leukopenia, by cohort.

	All		Cohort							
			.		Initial system		Current system, new patients		Current system, old patients	
	n	%	n	%	n	%	n	%	n	%
Sex										
F	153	38.25	2	100.00	34	39.53	105	37.77	12	35.29
M	247	61.75	.	.	52	60.47	173	62.23	22	64.71
Age groups										
<=35	126	31.50	1	50.00	27	31.40	86	30.94	12	35.29
36-50	158	39.50	.	.	40	46.51	101	36.33	17	50.00
51-65	101	25.25	.	.	19	22.09	77	27.70	5	14.71
>65	15	3.75	1	50.00	.	.	14	5.04	.	.
Race										
AFRO-CARIB	22	5.50	.	.	4	4.65	17	6.12	1	2.94
ASIAN	21	5.25	.	.	4	4.65	16	5.76	1	2.94
CAUCASIAN	353	88.25	.	.	78	90.70	243	87.41	32	94.12
MIXED	4	1.00	2	100.00	.	.	2	0.72	.	.

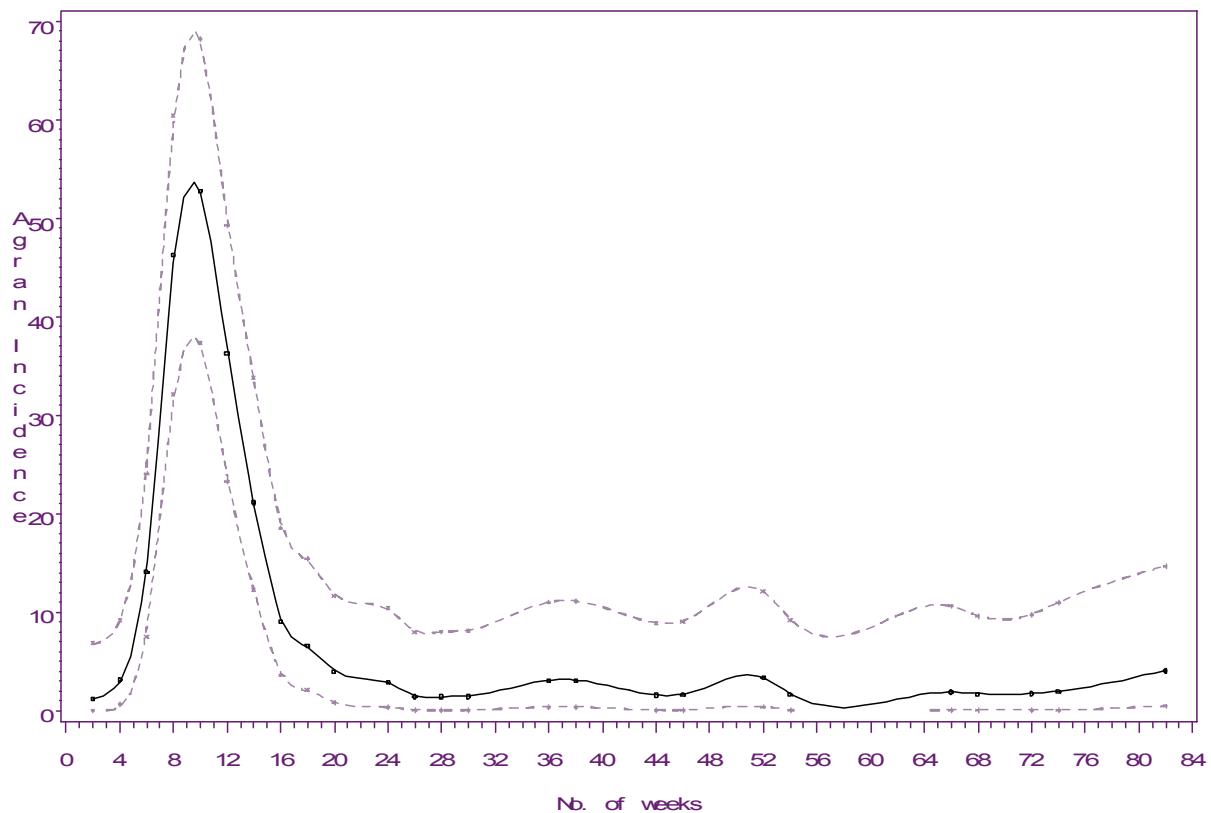
24 Demographic characteristics of the UK CPMS patients with red alert, by cohort.

Table 4.24. Demographic characteristics of the UK CPMS patients with red alert, by cohort.

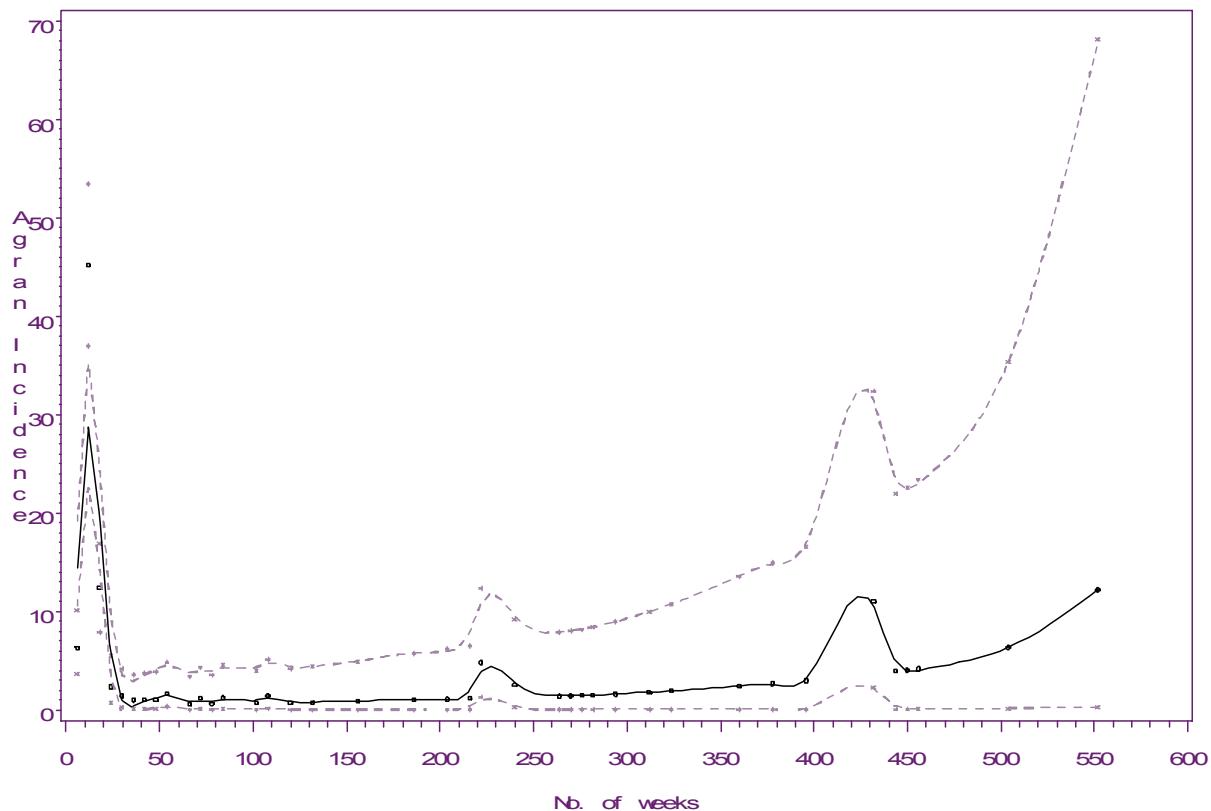
	All		Cohort							
			.		Initial system		Current system, new patients		Current system, old patients	
	n	%	n	%	n	%	n	%	n	%
Sex										
F	528	39.34	3	100.00	136	40.24	348	39.23	41	35.96
M	814	60.66	.	.	202	59.76	539	60.77	73	64.04
Age groups										
<=35	645	48.06	1	33.33	173	51.18	419	47.24	52	45.61
36-50	433	32.27	1	33.33	109	32.25	274	30.89	49	42.98
51-65	226	16.84	.	.	53	15.68	161	18.15	12	10.53
>65	38	2.83	1	33.33	3	0.89	33	3.72	1	0.88
Race										
AFRO-CARIB	160	11.92	.	.	28	8.28	126	14.21	6	5.26
ASIAN	53	3.95	.	.	8	2.37	38	4.28	7	6.14
CAUCASIAN	1108	82.56	1	33.33	297	87.87	711	80.16	99	86.84
MIXED	19	1.42	2	66.67	5	1.48	11	1.24	1	0.88
ORIENTAL	2	0.15	1	0.11	1	0.88

Figures

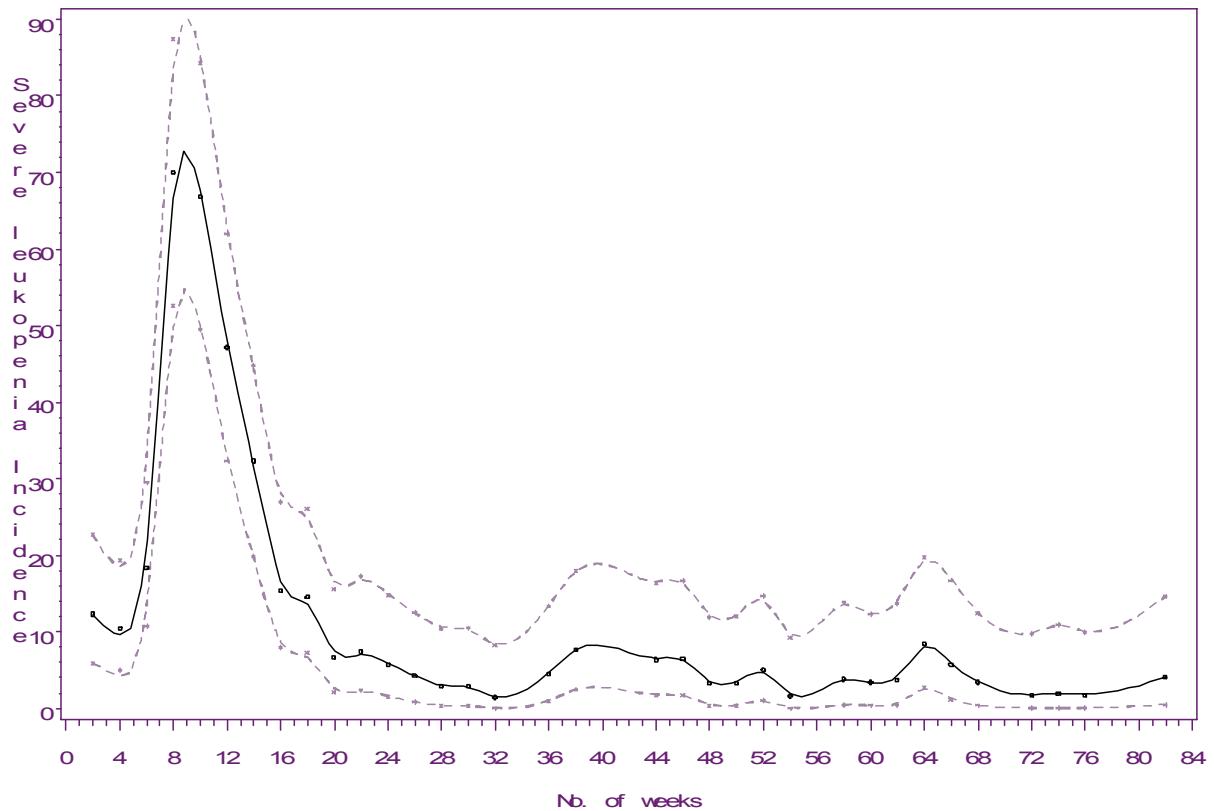
1) Agranulocytosis incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).



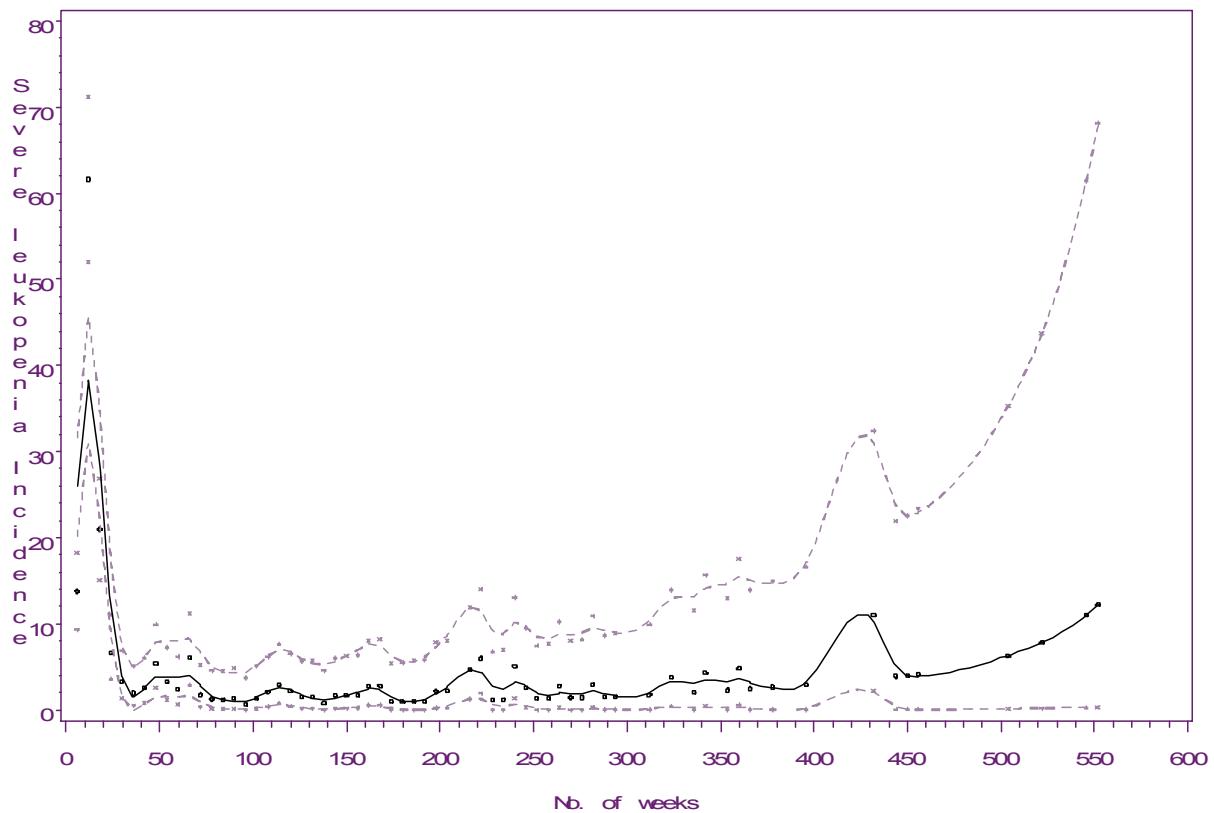
2) Agranulocytosis incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).



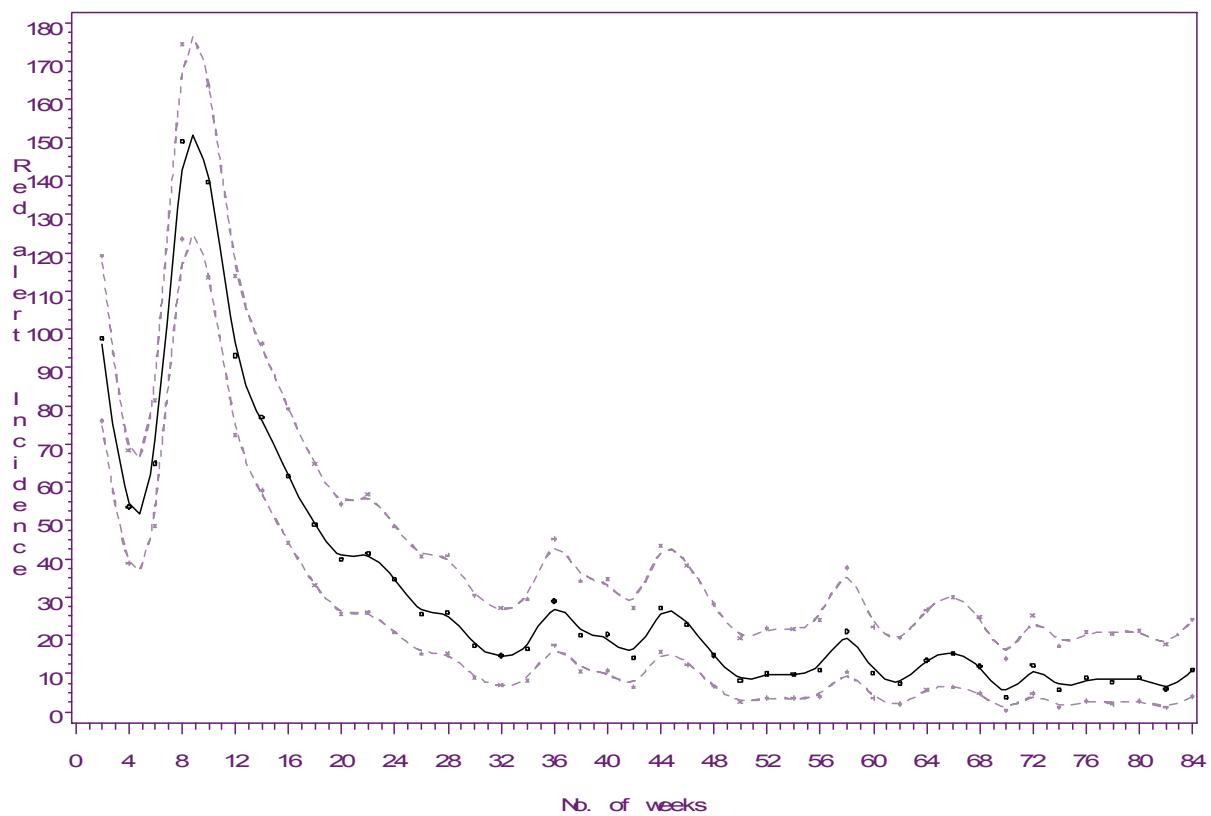
3) Severe leukopenia incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).



4) Severe leukopenia incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).



5) Red alert incidence per 1,000 person years and 95% CI, for the first 84 weeks of treatment (in 2-week intervals).



6) Red alert incidence per 1,000 person years and 95% CI, by treatment duration (in 6-week intervals).

