1 SUMMARY AND CONCLUSIONS

The SEROQUEL Core Data Sheet (CDS) notes that there is the possibility of 'limited' weight gain, predominantly during the early weeks of treatment, associated with SEROQUEL treatment as a possible adverse reaction. After considering the available short-term and long-term clinical trial data, in addition to post-marketing safety data, regarding changes in weight seen with SEROQUEL treatment, it is recommended that section 4.8 of the Core Data Sheet (CDS) be changed as follows:

Remove: *"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment"*

Add: *4.8 Possible adverse reactions*

"As with other antipsychotics, SEROQUEL may also be associated with weight gain. This occurs predominantly during the early weeks of treatment"

The reason for this change to the core labeling is that the original description of limited weight gain in the CDS implied that significant weight gain did not occur in patients treated with SEROQUEL. However, it has become more apparent that a small number of cases of significant weight gain been has reported in patients treated with SEROQUEL.

2 BACKGROUND

The purpose in conducting this review was to determine whether the qualifier 'limited' was accurate and should remain in the above statement in the CDS, based on the latest analyses of weight change in patients treated with SEROQUEL.

3 LITERATURE

A literature search was conducted for reports of weight gain in published comparative clinical studies of SEROQUEL in patients with psychotic disorders. The quality and quantity of information obtained in these reports was insufficient to assess what role, if any, SEROQUEL may have played in causing weight gain. Weight gain was not a primary end point of any of these studies. No report provided individual patient values for weight gain. Most reports only cited the mean weight change of the groups.

4 CLINICAL TRIAL DATA

The latest analysis of weight change in patients treated with SEROQUEL is based on weight data from controlled and uncontrolled clinical trials of SEROQUEL and the respective open-label extension studies. SEROQUEL was the only antipsychotic medication allowed throughout the double-blind and open-label extension phase of each study. The dose of SEROQUEL throughout was flexible, up to a maximum of 800 mg/day. All patients had a DSM-IV diagnosis of schizophrenia. Patients with psychotic symptoms were evaluated for eligibility to enter the controlled and uncontrolled studies of SEROQUEL according to the inclusion and exclusion criteria of the particular study. Weight was assessed at baseline and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months.

The results from the analysis presented below have been published in the literature (Brecher et al, 2000).

The mean weight change over 18 months' treatment with SEROQUEL is presented in Table 1.

Table 1 Mean weight change in patients treated with SEROQUEL over 18 months

Treatment period (weeks)	N	Mean weight change from baseline (Kg)
9 to 13	170	1.58
14 to 26	165	0.26
27 to 39	134	1.66
40 to 52	41	-1.53
53 to 78	146	1.94

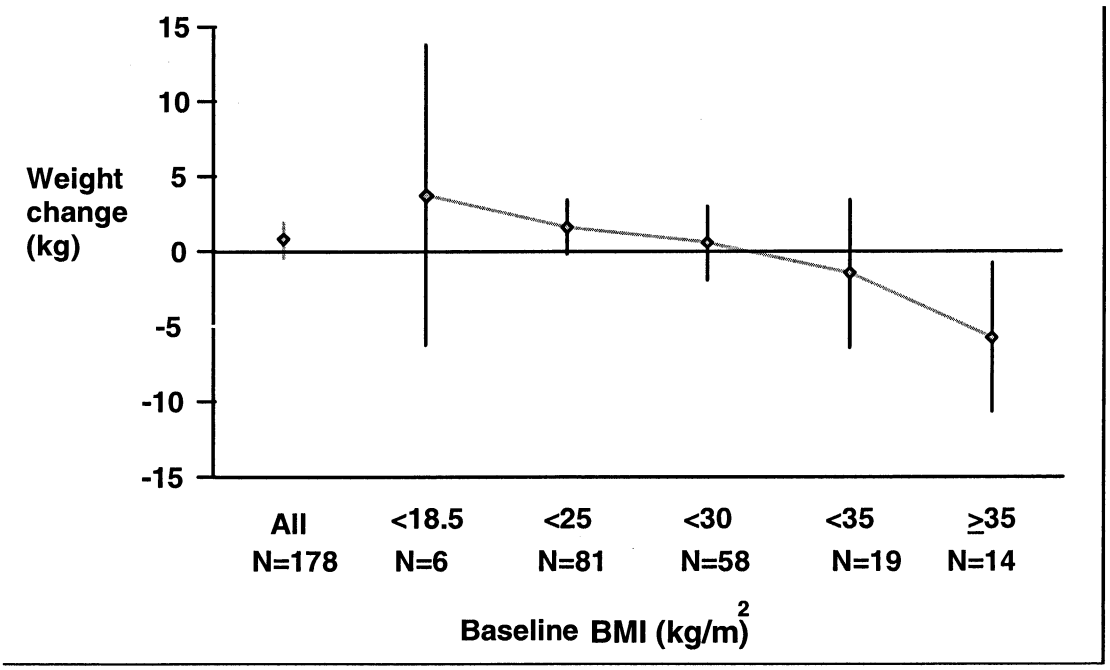
To specifically assess the long-term effect of SEROQUEL on weight, weight changes were calculated in those patients who had received at least 6 months' treatment with SEROQUEL. These patients were stratified into categories according to their body mass index (BMI) at baseline (patients were grouped according to the National Institutes of Health National Heart, Lung and Blood Institute's standard categories for BMI).

The mean changes in weight from baseline to endpoint for patients in each BMI category, together with 95% confidence intervals, are presented in Table 2 and Figure 1.

Table 2 Weight changes from baseline to endpoint by baseline BMI category in patients treated for at least 6 months with SEROQUEL monotherapy

Baseline BMI (kg/m^2)	N	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)	95% confidence intervals
All	178	473	563	0.41	-0.918, 1.742
< 18.5	6	443	540	3.75	-6.227, 13.777
≥ 18.5 and < 25	81	468	539	1.6	-0.212, 3.422
≥ 25 and < 30	58	466	607	0.53	-1.891, 2.946
≥ 30 and < 35	19	514	551	-1.53	-6.480, 3.417
≥ 35	14	483	543	-5.76	-10.670, -0.840

Figure 1 Weight changes from baseline to endpoint by baseline BMI category in patients treated for at least 6 months with SEROQUEL monotherapy



≥26 weeks of treatment, mean duration 18.6 months, N=178, mean daily dose 473 mg

The mean weight change following short-term treatment with SEROQUEL (9 to 13 weeks) was 1.58 kg. This is consistent with the short-term weight data (≤ 6 weeks) from the latest integrated clinical trials safety database for SEROQUEL.

The overall mean weight change following at least 6 months' treatment with SEROQUEL was small (+ 0.41 kg). The 95% confidence interval for this weight change included zero, indicating that the weight gain was not statistically significantly different from baseline. Weight changes across all BMI categories were small, with 95% confidence intervals overlapping the zero change line in all but the severely obese patients (baseline BMI ≥ 35 kg/m^2; a mean decrease in weight was observed in these patients). In summary, long-term treatment with SEROQUEL showed no overall effect on weight, except in severely obese patients in which a mean decrease in weight was noted. The results of this analysis of the clinical trial data therefore appeared to justify or support retention of the word "limited" in the CDS. It was then necessary to consider our Clintrace Database.

5 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

There were a total of 117 events of weight gain of which 111 were from spontaneous sources and 6 from literature sources regarding weight gain associated with SEROQUEL therapy. These do not include clinical trial sources. There were 2 cases where weight gain was reported to be a serious event and 115 non-serious weight gain events. There were 76 medically confirmed reports received from health professional reporters and considered relevant and approximately 41 of the 111 spontaneous reports were received from consumers or their family members.

The total of 117 patients ranged in age from 8 to 70 years of age with a mean of 38 years (median = 38 years). There was a modest female predominance with females constituting 59% of patients in reports in which gender was specified. There were 69 females, 37 males and the remaining eleven cases did not mention gender. In the 76 medically-confirmed reports there were 44 females and 22 males. 10 reports did not specify gender. Age was specified in 48 of the 76 reports and ranged from 8 to 69 (average and median 34).

The total reported weight gain ranged from 1.98 pounds (0.9 Kg) to 100 pounds (45 Kg) with the average reported weight gain being 32 pounds (14.5 Kg) and the median reported weight gain being 30 pounds (14 Kg). 64 of the 117 cases included specific information on the amount of weight gained. Obtaining the time interval between date of initial therapy and the date of onset of weight gain was often not possible due to reported approximations given in terms of months without the day provided. In these cases, it was not possible to determine the time. Otherwise, when an exact day was provided and the onset occurred within the same month the time designated for onset was the difference between the total days of the month listed and the actual event start date provided. Such information, allowing an exact or approximate number of days,

was provided in 36 of the 117 reports. Of the cases with a known number of days from first dose to the start of the weight gain, the time interval between initial therapy and the date of onset of the reported event ranged from one day to 850 days. The average time to onset of weight gain after starting treatment with SEROQUEL was 74 days with a median of 30.

Similar to the demographics concerning all 117 reports, of the 76 medically confirmed cases, the reported weight gain ranged from 1.98 pounds (0.9 Kg) to 100 pounds (45 Kg) with the average reported weight gain being 32 pounds (14.5 Kg) and the median reported weight being 30 pounds (14 Kg). Of the 76 medically confirmed cases, 40 included specific information on the amount of weight gained and 24 cases included the time interval between initial therapy and the date of onset of the reported weight increase. Many of the unquantified cases provided the total weight gain over a time period; however, the start date of the event was not provided. Of the cases with a known number of days to onset, the time interval between initial therapy and the date of onset of the reported event ranged from 1 day to 850 days. The average time to onset of weight gain after starting treatment with SEROQUEL was 75 days with a median of 30 days. There were two reports (1999AP02974 and 1999UW02120) describing a negative dechallenge in which the accrued weight was not lost following SEROQUEL discontinuation.

Confounding factors: Five patients developed edema (2001AP03515, 2000UW02110, 2000UW01802, 1999UW01496 and 1998UW46392), and one patient (1999AP00761) was diagnosed with congestive heart failure. These conditions are also known to contribute to weight gain secondary to fluid retention and accumulation. Water retention was additionally reported in three cases (2001UW15857, 2001UW14243 and 2000UW00745). In case 2001UW06111 there was a reported history of fluid retention and the patient was receiving concomitant treatment of Lozide for edema. Several reports contained scant information which precluded detailed analysis of these cases.

Fourteen patients were receiving concomitant medication associated with weight gain (2001UW09521,Clozaril; 2001UW08005, Depakote; 2001UW02873,Clozaril; 2001UW00844, Depakote; 2001UW00231, Zyprexa; 2001UW05269, Risperdal; 2000UW02110, Mellaril; 2000UW01802, Remeron; 2000UW01551, risperidone; 2000UW01004, valproic acid; 1999UW03900, Zyprexa and Eskalith; 1998UW48690, Depakote and Risperdal; 1998UW47193, Paxil; 1998UW46392, Depakote). Patient 2001UW05269 may have discontinued risperidone.

Four patients (1999UW02120, 1998UW48690, 2001UW05633 and 2001UW00844) had concomitant hypothyroidism, a known cause of weight gain. In addition, one patient (1999AP05242) developed hypothyroidism after starting SEROQUEL treatment. Another patient (2000AP01643) developed abnormal thyroid test, which resolved when SEROQUEL was discontinued. According to the SEROQUEL CDS: *SEROQUEL treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4... with*

no indication that SEROQUEL causes clinically relevant hypothyroidism. It is possible that small dose-related decreases in thyroid hormone levels could result in weight gain, however this does not explain the negative dechallenge described above in which the patient's weight increase persisted despite discontinuing SEROQUEL. Nor does it explain the average time interval between the start of therapy with SEROQUEL and the date of the reported weight gain in post-marketing reports.

There were 5 reports of positive dechallenge (1999PK01108, 1999UW01496, 2000AP04967, 2000UW00595, and 2001UW15857) and no positive rechallenges.

6 DISCUSSION AND CONCLUSION

In the course of extensive post-marketing exposure to SEROQUEL, 117 reports of weight gain were received by AstraZeneca. The quality and quantity of information obtained from reporters of these cases were often suboptimal to assessing what role, if any, SEROQUEL may have played in causing the weight gain. In particular, it is known that treatment for schizophrenia with more than 1 antipsychotic is common, yet whether the patient in each case received additional antipsychotics, or indeed other concomitant medications, was often not specified. (This information is important, as other medications, particularly antipsychotic therapies, vary in the extent to which they may cause changes in body weight.) Also, in many cases the amount of weight gain was not specified. Furthermore, in many cases it was not noted whether the patients had a previous history of weight gain, and none of the cases were assessed on the basis of patients' baseline BMIs. (BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height.) Finally, it was also noted that some of the patients had concomitant illnesses that could have caused weight gain.

The latest results from the clinical trial database are based on analyses of prospective clinical trial data documenting weight change associated with SEROQUEL. In particular, only data from patients who received SEROQUEL monotherapy were included in the analyses, and weight change in the long-term was assessed in relation to the patients' initial BMI. Weight gain of 1 to 3 kg during the first months of treatment is similar to all marketed antipsychotics; this is indicated in the current CDS. Data from the Phase II/III comparator-controlled trials in the latest integrated safety database for SEROQUEL show that short-term weight gain was reported as an adverse event in only 1% of SEROQUEL, haloperidol and risperidone patients and was a reason for discontinuation in only 1 (0.1%) SEROQUEL patient.

Agree with that statement

The original description of limited weight gain in the CDS implied that significant weight gain did not occur in patients treated with SEROQUEL. However, it has become more apparent that a small number of cases of significant weight gain have been reported in patients treated with SEROQUEL.

Recommend Change on following Page

Therefore, it is recommended that section 4.8 of the CDS be changed as follows:

Remove: *"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment"*

Add: *"As with other antipsychotics, SEROQUEL may also be associated with weight gain. This occurs predominantly during the early weeks of treatment"*

References

Brecher M, Rak IW, Melvin K, Jones AM. The long-term effect of quetiapine (Seroquel) monotherapy on weight in patients with schizophrenia. International Journal of Psychiatry in Clinical Practice 2000; 4: 287-291