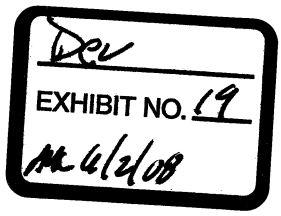

DISCUSSION DOCUMENT

SEROQUEL™

WEIGHT GAIN

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

SERM NO 32 - 22 JUNE 2000 - MINUTES

Participants: M Brecher

After review of the available data SERM considered that the descriptor 'limited' should be removed from the CDS.

ACTION - WG create a justification document

AUTHOR(S):

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SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

The SEROQUEL Core Data Sheet (CDS) notes that there is the possibility of "limited" weight gain associated with SEROQUEL treatment. Consideration should be given to removing the qualifier "limited" based upon data from the Clintrace database (postmarketing safety data) and after analyzing reports of weight gain from clinical trials not contained in the Clintrace database (not meeting seriousness criteria).

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for SEROQUEL and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for SEROQUEL for their review. This discussion document will specifically focus on FDA's request that AstraZeneca perform "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycemia, hyperosmolar coma, diabetic ketoacidosis, and *weight gain*".

2 BACKGROUND

The SEROQUEL CDS last revised in March 2000 does not include listings for NODM, hyperglycemia, NKHOC, or DKA. Weight gain is a listed event for SEROQUEL and is contained in the CDS:

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

The SEROQUEL US package insert (PI) includes weight gain as a labelled event. In addition to FDA's request, the purpose in conducting this review is to determine whether the existing labeling in the CDS is accurate based upon the number and types of reports of weight gain received to date. Reference to weight gain as it pertains to glucose regulation will not be mentioned in this discussion document, but instead will be commented on in a separate discussion document presented at this SERM reviewing diabetes mellitus, diabetic ketoacidosis, non-ketotic hyperosmolar coma, and hyperglycemia.

3 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which weight gain was reported with SEROQUEL. Narratives are provided for 42 reports.

Case Number: 1999UW03900

WEIGHT GAIN

A report has been received from a registered nurse concerning her 47 year old female daughter who has been receiving SEROQUEL 800 mg daily for schizoaffective disorder, since the fall of 1997. Since May 1999 she started gaining weight (around 40 lbs). Patient is also receiving eskalith, prozac and zyprexa. Patient's physician is not concerned about the weight gain, since patient is responding well to SEROQUEL. No other information available.

Case Number: 1999UW03722

DRY SKIN, INCREASED SLEEP, INCREASED WEIGHT, VIVID UNSETTLING DREAMS

A report has been received from a patient who is taking SEROQUEL 700 mg daily, and is experiencing dry skin on his scalp and "membranes, etc," vivid and unsettling dreams, increased sleep "up to 50%," and increased weight by 20 to 30 lbs. The patient had noticed all of these events while previously taking amitriptyline with the exception of weight gain. The patient states that the events have improved after six months, and that nicotine has helped the sleep problem. No follow-up is expected.

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving SEROQUEL and developed diabetes. Physician feels that SEROQUEL may possibly be responsible for the development of diabetes.

Follow-up 11 November 1999: Physician reports that the 47 year old female (not 45) had been receiving SEROQUEL 600 mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues it has improved. SEROQUEL was tapered for discontinuation. Concomitant medications include klonopin and benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "SEROQUEL caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW02762

INCREASED HUNGER, WEIGHT GAIN, STUPOR, ELEVATED CPK, ELEVATED SGPT

A report has been received from a 44 year old male patient who has been receiving SEROQUEL 25 to 50mg daily and has experienced increased hunger resulting in a 30 lb weight gain in six months. The patient also reports that he wakes in a "stupor" even when he takes only 25mg.

Follow-up 27 July 1999: Consumer reports that when he exercises he experiences an elevation in his creatine phosphokinase level (increased to 4600) and his SGPT (alanine aminotransferase) levels. He reports that after no activity for two weeks his enzymes return to normal.

Case Number: 1999UW02683

SLEEPINESS, WEIGHT GAIN

A report has been received from a 63-year-old female patient who has been receiving SEROQUEL 300 mg daily. The midday dose of SEROQUEL 100 mg really "wipes her out" (makes her sleepy).

*Follow up 26 July 1999: The patient reports that she has gained 3 pounds since starting SEROQUEL. With her nighttime dose of SEROQUEL she also takes luvox, klonopin, and vistival and in the morning she is very sleepy.

Case Number: 1999UW02297

WEIGHT GAIN

Wyeth Ayerst forwards the following information: A report has been received from a female patient who has been receiving SEROQUEL and gained 35 pounds.

Case Number: 1999UW02120

WEIGHT GAIN, SUICIDE IDEATION, DEPRESSION

A report has been received from a female patient who began receiving SEROQUEL on 20 May 1999 and gained five pounds in ten days.

*Follow up 04 June 1999: Patient said her problem was a hypothyroid disorder. Patient also takes lithium and diazepam. She discontinued the lithium against her physician's orders.

*Follow up 09 June 1999: Patient reports that she feels that her hypothyroid condition is due to Lithium, not SEROQUEL, but she still feels her weight gain is due to SEROQUEL.

*Follow up 16 June 1999: Wyeth Ayerst provides the following information: The patient reports that while taking SEROQUEL she has experienced a five pound weight gain in ten days and feels this drug has caused her thyroid to stop working.

*Follow up 17 June 1999: The patient reports that she started SEROQUEL on 20 May 1999 and discontinued it 31 May 1999. During that time she gained 5 pounds which she cannot lose. She is 5¿1" and normally weighs 105 lbs and now weighs 110 lbs. Her physician tested her thyroid and it was found to be within normal limits. She is concerned that SEROQUEL has affected her metabolism. She states that she will not live if she gains weight and cannot lose it and is contemplating suicide.

*Follow up 18 June 1999: Patient further reports that she has been to a nutritionist and her physician and they do not know if she will lose the additional weight. She said this is adding to her depression.

Case Number: 1999UW01986

WEIGHT GAIN

A report has been received from a physician concerning an unidentified patient who is receiving SEROQUEL 300 mg daily and has experienced a 20 pound weight gain. More information will be requested.

Case Number: 1999UW01797

WEIGHT GAIN

A report has been received from a nurse concerning her 46-year-old daughter who has been receiving SEROQUEL 200 mg four times daily for a schizoaffective disorder since September 1998. She has experienced a weight gain of approximately 30 pounds since starting SEROQUEL.

Case Number: 1999UW01496

SEDATION, DIZZINESS, MUSCLE STIFFNESS, DISTURBANCE OF THOUGHTS, LOSS OF BALANCE, WEIGHT GAIN, EDEMA IN ANKLES AND FEET, EDEMA IN HANDS, ELEVATED INCREASED TRIGLYCERIDE LEVEL

A report has been received from a consumer concerning her husband a 46 year old male patient who has been receiving SEROQUEL (at increasing doses) and lithium for bipolar disorder since October 1998 and is experiencing varying degrees of sedation, dizziness and muscle stiffness among other symptoms. These symptoms subside with time but reoccur at increasing dosages of SEROQUEL. The reporter states "that the most disturbing side effects, the symptoms for which

SEROQUEL is being used, are getting worse ("thought broadcasting" from inside his head)." The patient has better control of his symptoms and less side effects with SEROQUEL at 50 mg daily. At 300 mg daily, he experiences loss of balance, severe sedation, stiff muscles and cannot drive. The patient is now receiving 250 mg of SEROQUEL daily.

Follow-up 30 November 1999: Consumer reports that (her husband) the patient's dose of SEROQUEL has been reduced to 100 mg due to a weight gain of 70 pounds, edema in his ankles, feet and hands, and a high triglyceride level (2000). The patient was treated with lasix for the edema which has improved in his hands but not his feet and ankles. Since the dosage has been reduced, the patient has lost 10 pounds. His physician has introduced haldol as the SEROQUEL dosage is decreased.

Follow-up 05 January 2000: Consumer reports that (her husband) the patient discontinued SEROQUEL in December 1999 and has been receiving diuretics. He has lost 30 pounds and the edema has also improved.

Case Number: 1999PK01108

DIPLOPIA, SWEATING, HEADACHE, WEIGHT GAIN, TREMBLING INSIDE, TENSENESS

A report has been received from a physician concerning a 35 year old female patient who has received SEROQUEL for treatment of schizophrenia outside a clinical trial. There was no concomitant medication. The therapy began at the end of May 1999. The patient developed sweating, headache, weight gain, trembling inside and tenseness in the beginning of July and diplopia in mid October. Following dose reduction all adverse events have been improving. The reporter considered a causal relationship with SEROQUEL due to the temporal course.

Case Number: 1999AP05794

INCREASED APPETITE, WEIGHT GAIN

Case Number: 1999AP05792

INCREASED APPETITE, WEIGHT GAIN

Case Number: 1999AP05757

DIABETES, KETOACIDOSIS.

A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750 mg daily for psychosis since November 1997. He was receiving acamprosate, depixol and priadel concomitantly.

In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing. The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for quetiapine fumarate.

Case Number: 1999AP05734

INCREASED APPETITE, WEIGHT GAIN

Case Number: 1999AP05733

SEDATION, INCREASED APPETITE, WEIGHT GAIN

Case Number: 1999AP05242

HYPOTHYROIDISM, WEIGHT GAIN

Case Number: 1999AP04948

DISTURBED SLEEP, WEIGHT GAIN

Case Number: 1999AP04348

WEIGHT GAIN

Case Number: 1999AP04331

WEIGHT GAIN

Case Number: 1999AP04033

HIATUS HERNIA, OESOPHAGITIS

A report has been received from a physician concerning a 30 year old male patient who has been receiving SEROQUEL (400 mg/day) since September 1998.

The patient has a medical history of learning disabilities.

Approximately 3 months after starting SEROQUEL treatment, the patient experienced sickness and retching. An urgent endoscopy revealed that he had a hiatus hernia and oesophageal ulcer. He was also suffering from mild pericarditis which was deemed to be non-serious by a Zeneca physician. He was prescribed lansoprazole instead of ranitidine for the symptoms. The

physician was reluctant to stop SEROQUEL treatment as his patient was benefitting from the drug treatment. Therefore, treatment with SEROQUEL continued. The patient also experienced weight gain (non-serious) since starting SEROQUEL treatment. At the time this report was received the event is ongoing with reported worsening of symptoms. The reporting physician does not consider the events to be related to SEROQUEL treatment. However, the patient's G.P. feels that events may be related.

New Information Received 19 July 1999. The patient has a past medical history of oesophagitis. It is planned that SEROQUEL will be continued and the hiatal hernia, oesophagitis and pericarditis will be investigated to determine their cause.

Case Number: 1999AP03032

NUMBNESS AND TINGLING OF FEET, CARPAL TUNNEL SYMPTOMS

Case Number: 1999AP02974

WEIGHT GAIN

Case Number: 1999AP00761

CONGESTIVE CARDIAC FAILURE.

A report has been received from a physician regarding a 60 year old male patient with schizophrenia who has been receiving SEROQUEL (quetiapine fumarate) as treatment. The patient has a medical history of heart attack.

In September 1998, around the same time SEROQUEL therapy was started the patient began noticing a weight gain, he put on about 12 kg. In December 1998 a physical examination and x-ray showed severe congestive cardiac failure, an echocardiogram showed diminished ventricular function. On 01 February 1999 the patient died of congestive cardiac failure and ischaemic heart disease. SEROQUEL therapy was not discontinued before the patient died.

The reporter felt there was a reasonable possibility that the events were related to SEROQUEL therapy.

Case Number: 1998UW49851

TARDIVE DYSKINESIA, SEDATION, STIFFNESS IN NECK, WEIGHT GAIN

A report has been received from a 60 year old female patient who after being titrated to 200 mg daily of SEROQUEL experienced tardive dyskinesia, severe sedation, stiffness in her neck and a weight gain of ten pounds. The patient has been receiving SEROQUEL for approximately two

months. The dosage was decreased to 25 mg daily and the tardive dyskinesia has decreased in severity

Case Number: 1998UW48690

WEIGHT GAIN, SLEEPY, HALLUCINATIONS

A report has been received from the husband of a 70-year old female consumer who is receiving SEROQUEL 125 mg daily for treatment of bipolar disorder. The patient is experiencing weight gain and is very sleepy. She is also still seeing bugs crawling about. Her physician gave her 0.5 mg of risperidol to help the hallucinations. The patient is a diabetic and is wheelchair bound. She has high blood pressure and memory loss. She has been in and out of the hospital for 40 years being treated with various antipsychotic medications. Currently the patient takes Synthroid .088 mg daily, depakote 500 mg three times daily, risperidol 0.5 mg, baby aspirin 81 mg, rezulin, glipizide and premprol.

Case Number: 1998UW47692

SEDATION, WEIGHT GAIN

A report has been received from a nurse, who is also the 50 year old female patient, who is taking SEROQUEL 25 mg daily, and has experienced sedation and weight gain.

Case Number: 1998UW47347

RASH, CONSTIPATION, WEIGHT GAIN.

A report has been received from a the mother of a 40-year old male patient who has been taking SEROQUEL for two months and is now up to 600 mg daily. The patient is experiencing a rash, which may be seasonal because he has had it off and on for three years. He also experiences constipation to the point of being impacted and had gained 30 pounds.

Case Number: 1998UW47193

WEIGHT GAIN

A report has been received from a 45 year old female who has been receiving SEROQUEL (indication unknown) since March 1998 and has gained 20lbs. She currently takes 100 mg in the morning and 175 mg at night. She states she hasn't changed her eating habits or any other medications. Patient is also receiving valium, paxil and ogen.

Case Number: 1998UW47126

INCREASED APPETITE, WEIGHT GAIN, PAIN IN UPPER ARMS

A report has been received from a 57 year old male patient who has taken SEROQUEL 100 mg twice daily for two months (since April 1998). The patient has experienced an increased appetite, weight gain and severe pain in his upper arms "like a charlie horse". The patient takes various concomitant medications but only mentioned norvasc (because he thought norvasc caused muscle cramps too).

Case Number: 1998UW46805

MOOD SWINGS, PSYCHOTIC BEHAVIOUR, SUICIDAL EVENTS, LACTATION, WEIGHT GAIN

A report has been received from a nurse concerning her 22 year old daughter who has been on SEROQUEL 50 mg twice daily since January 1998 and during her last two menstrual cycles experienced severe mood swings and psychotic behavior, including suicidal episodes, for which she was hospitalized. She also had some lactation during this period. Patient has a history of self mutilation and had taken risperdal prior to taking SEROQUEL, but this was discontinued due to a 20 pound weight gain in one month and elevated prolactin level. Patient also takes paxil 10 mg daily, wellbutrin 150 mg daily, and lamictal 50 mg twice daily. *Follow up 29 June 1998: The patient took SEROQUEL 50 mg twice daily from January 1998 to 11 June 1998 for borderline personality disorder. Her dose had been adjusted periodically. In June 1998 her prolactin level was 36. It was the reporter's opinion that poor continuity of care was the cause of the reported conditions.

Case Number: 1998UW46392

EDEMA, VASCULAR MARKINGS ON LEGS, POSSIBLE DRUG INTERACTION WITH DEPAKOTE, WEIGHT GAIN.

A report has been received from a nurse practitioner concerning a 33 year old female who had been taking SEROQUEL 300 mg from December 1997 to 11 February 1998. In December 1997 she began to experience 2 to 3 + pitting edema, vascular markings on her legs (like stripes), and weight gain. She was also taking depakote 1000 to 1500 mg from September 1997 to February 1998. Reporter was wondering if there was a possible drug interaction with SEROQUEL and depakote. Her symptoms have not resolved. Patient also takes triphasil (levonorgestrel) and effexor (venlafaxine hydrochloride). CAT scan, sonogram, EKG, and liver function tests were given; all tests were normal. She has no known allergies.
*Follow up 19 May 1998: Physician states patient had 2 to 3 + edema which began

on 07 February 1998 that continues but is improved. The patient developed severe vascular markings on legs and arms on 01 December 1997 and recovered fully on 01 April 1998. Patient experienced a 50 pound weight gain since 01 December 1997 that has not resolved. Physician feels depakote "seems to be the culprit."

Case Number: 1998UW45402

WEIGHT GAIN, SLEEPINESS, COULD NOT SWALLOW, VIVID DREAMS, AROUSED.

A report has been received from a 34-year old male patient who received SEROQUEL as part of a clinical study from December 1997 through March 1998. During this time the patient experienced weight gain, sleepiness, he could not swallow when he took the pill at dinner, had vivid dreams and woke in the morning aroused. The patient has discontinued the SEROQUEL due to the weight gain.

Case Number: 1998UW43797

WEIGHT GAIN, AMENORRHEA.

A report has been received from a physician concerning a female patient who was receiving SEROQUEL 200 mg daily since 26 December 1997. she gained 15 pounds and has not had a period for two months. Patient started depakote in June 1997 and had not gained weight from it prior to December 1997.

Case Number: 1998AP50136

WEIGHT GAIN

Case Number: 1998AP49255

SLURRED SPEECH, SEDATION, INCREASED APPETITE, WEIGHT GAIN.

Case Number: 1998AP49247

WEIGHT GAIN

Case Number: 1998AP48883

CONSTIPATION, WEIGHT GAIN, DROWSINESS

Case Number: 1998AP48866

WEIGHT GAIN, DROWSINESS

Case Number: 1998AP46732

WEIGHT GAIN

Follow up information received on 22 December 1998:

Patient is still taking SEROQUEL 400 mg/d and putting on weight. Patient is being monitored.

Case Number: 1998AP46146

WEIGHT GAIN

Case Number: 1998AP45681

WEIGHT GAIN, AMENORRHOEA

4 DISCUSSION

There were 38 spontaneous reports and 4 literature reports of weight gain associated with SEROQUEL therapy. None of these were from clinical trials. Approximately 23 of the 38 spontaneous reports came from consumers or family members thereof. Patients ranged in age from 8 to 70 years of age with a mean of 38 years (median = 36 years). There is a slight female predominance with females constituting 55% of reports in which gender was specified. Reported weight gain ranged from 2 pounds (0.9 kg) to 70 pounds (31.8 kg) with the average reported weight gain being 27.6 pounds (12.5 kg) and the median reported weight gain being 23.5 pounds (10.7 kg). The average time interval between initial therapy and the date of the reported event was 6.8 months with a median of 4 months. The range was 10 days (5 pounds; 2.3 kg) to 2 years (40 pounds; 18.2 kg).

Confounding factors: Two patients developed edema (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. There was one report (1999UW02120) describing a negative dechallenge in which the accrued weight remained following SEROQUEL discontinuation. Several reports contained scant information which precluded detailed analysis of these cases.

Two patients (1999UW02120 and 1998UW48690) had concomitant hypothyroidism, a known cause for weight gain. In addition, one patient (1999AP05242) developed hypothyroidism after starting SEROQUEL treatment. 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 initial SEROQUEL therapy and the date of the reported weight gain (6.8 months; median = 4 months) in postmarketing reports.

While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that SEROQUEL therapy can produce significant weight gain in select individuals. The SEROQUEL CDS mentions the possibility of "limited" weight gain associated with SEROQUEL treatment, however consideration should be given to removing the qualifier "limited" based upon postmarketing and clinical trial safety data.