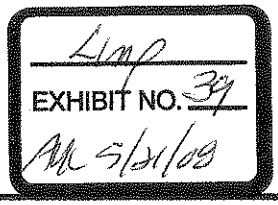

Goldstein, Jeffrey M

From: Replenski, Lois on behalf of Bowen, Rebecca
Sent: Wednesday, November 06, 2002 2:14 PM
To: +CNS TA MANAGEMENT Team; Altman, Charles; Hagger, Simon; Hess, William; Lapp, Carrie; Sayce, Rod; Swalley, Jeffrey S; Wilkie, Alison M; Wright, Tim; Zimmerman, Paul M; Singh, Gurdish S; Litherland, Theresa; Ney, Christine A; Olbrich, Richard; Owen, Richard T; +Seroquel Global Product Team; +Seroquel Marketing Managers; +Seroquel Medical Managers; +Seroquel Product Managers; Minnick, Jim G; Heik-Schlaeger, Irene HS; Demerbe, Maryvonne; Rejholcova, Magda; Melichar, Lubos; Vedsø, Mette; Ahtila, Sirpa; Hache, Christine; Müller-Menke, Claudia; Moissidou, Athina; Berta, Gábor; Galligan, Olive; Lecchi, Daniela; Koomen, Oscar; Clemm, Christian; Mazur, Jaroslaw; Gomes, Fatima; Tregerova, Viera; De Navascues, Almudena; Pernvi, Christina; Billeter, Madeleine; Ulas, Koksal; Smith, Pam; Grafford, Kerstin; Horowitz, Anne M; Nemeth, Paul; McKenna, Kevin; Limp, Gerald L; Street, Paul R; Trumble, Sharon M; Parish, Caroline; Greatorex, Anthony; Harrison, Ali; Gore, Eileen; Satory, Markus; Heik-Schlaeger, Irene HS; Verstraeten, Véronique; Williams, Dilys; Rejholcova, Magda; Thuesen, Lars Ulriksen; Heiskanen, Paula; Knappe, Thomas; Bouga, Elina; Briët, Bregje; Balázs, Mihály; Gudmundsdóttir, Vera; Sigvaldadottir, Eydis; Griffiths, Jonathan; Berlingozzi, Savina; Carbines, Michelle; Coutts, Jennifer; Bergersen, Anne Gro; Niewiadomski, Piotr; Fonseca, Mecia; Tregerova, Viera; Vojtkova, Monika; Mbatha, Innocentia; Kriel, Esther; Legorburu, Maria-Jose J; De Navascues, Almudena; Astecker, Ernestine; Sorgun, Sena; Griffiths, Jonathan; Grafford, Kerstin; Horowitz, Anne M; Borg, Eleonor
Subject: URGENT - IMPORTANT INFORMATION ON LABEL CHANGES TO SEROQUEL IN JAPAN

Importance: High

SENT ON BEHALF OF REBECCA BOWEN

Dear Colleagues,

I would like to update you on the situation regarding label changes in **Japan.**

The MHLW (the regulatory authorities in Japan) will tomorrow (Thursday, November 7) impose a label change for Seroquel in Japan (marketed by our licensing partner Fujisawa). The label change is much more severe than we anticipated. They are also requiring Fujisawa to send out a 'Dear Doctor' letter to inform clinicians of the change and hold a press conference in Japan tomorrow. Both Japanese and international press will be present at this press conference.

This action follows the change to the label for Olanzapine in April this year.

Obviously this is very unexpected and disappointing news. **Based on the evaluation of our safety database, we do not believe that there is any evidence to suggest a causal relationship between Seroquel and glucose dysregulation, and we intend to defend this position.**

We would anticipate that the news from Japan will be picked up by the international press and will also be used by our competitors. It may also lead to proactive questions from regulatory authorities regarding our labelling. Please let us know as soon as these questions arise so that the global team can help provide you with the information required to respond to these questions.

I have attached an updated Q and A document to help you to respond to any questions that you may get.

Seroquel Diabetes QA - 6 Nov.d...

I have also included for your information only:

1/ Translation of the Seroquel label **before** the current changes

Original JPI.doc

2/ A translation of the Dear Doctor letter that will be sent out to clinicians in Japan which outlines the changes to be made in the Seroquel label

Quetiapine's dear Dr letter fo...

3/ A copy of the draft of the Japanese press release that is required to be sent out by AZKK (Japan). Please note that some further changes may be made to this prior to release, and if this is the case, any material changes will be communicated to you.

PRJAPDraft.doc

Please do not hesitate to contact Alex Oldham, Meg Melville (regulatory issues), or myself if you have any questions.

Any questions from analysts or journalists should be directed to Jim Minnick (Global PR manager) - +1 302 886 5135.

I would also appreciate it if you could let me know if and what type of questions you are getting in your market on this subject so that the Global Team can provide consolidated responses to such questions.

Kind regards

Rebecca Bowen
Global Marketing Director - Seroquel

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**Revised in July 2002 (4th edition)
*Revised in May 2002

Standard Commodity Classification No. of Japan
871179

	25 mg	100 mg
Approval number	21200AMY00239000	21200AMY00240000
Drug price tariff listing	February 2001	February 2001
Launch date	**February 2001**	**February 2001**
International Birthday	July 1997	July 1997

A drug for treatment of schizophrenia

Seroquel 25mg Tablet
Seroquel 100mg Tablet

(Generic name: quetiapine fumarate)

A powerful, designated, and prescription legend drug note

Note: Dispense only with a prescription or physician's direction.

Storage: This product should be stored at room temperature.

Expiry Date: Indicated on the package. (Three years from the date of manufacture)

[CONTRAINDICATION (Seroquel must not be given to the following patients.)]

(1) Patients in a coma (This product may aggravate coma.)
(2) Patients who are under the strong control of central nervous system depressants such as barbiturates, etc. (inhibitory action on central nervous system is enhanced.)
(3) Patients under the treatment of epinephrine (See "Drug Interactions".)
(4) Patients who have shown a hypersensitivity reaction to any component of Seroquel.

[COMPOSITION]

Trade Name	**Seroquel 25mg Tablet**			**Seroquel 100mg Tablet**		
Component and Quantity (as quetiapine per tablet)	Each tablet contains 28.78mg of quetiapine fumarate (25mg as quetiapine).			Each tablet contains 115.13mg of quetiapine fumarate (100mg as quetiapine).		
Colour and Formulation	Peach coloured-film coated tablets			Light yellow colour-film coated tablets		
Excipient	Macrogol 400			Macrogol 400		
Shape	Top	Back	Side	Top	Back	Side

	  	  
Diameter	About 6.0 mm	About 8.5 mm
Depth	About 3.5 mm	About 4.5 mm
Identification code	SEROQUEL 25	SEROQUEL 100
Weight	About 103 mg	About 256 mg

[INDICATION]

Schizophrenia

[DOSAGE AND ADMINISTRATION]

Usually in adults, a treatment should be started with an initial dose of 25mg of quetiapine, two or three times a day. The dose should be increased gradually based on the response of the patient. Normally, daily dosage should be 150 - 600mg, given orally in 2-3 divided doses. The dosage should be adjusted in accordance with the age and the response of the patient. The daily dosage should not exceed 750mg.

[PRECAUTIONS FOR USE]

1. Careful Administration (Seroquel should be administered with care to the following patients.)

(1) Patients with hepatic impairment [As quetiapine is extensively metabolised by the liver, the clearance may decrease and the blood concentration may increase. The treatment should be started with a small dose, such as 25 mg of quetiapine a day, then the dose should be gradually increased in increments of 25-50 mg/day to an effective dose, depending on the response in each patient. (See "PHARMACOKINETICS".)]

(2) Patients who are known or suspected to have cardiovascular disease, cerebrovascular disease or hypotension [Transient hypotension may develop during the initial dosing period.]

(3) Patients who have convulsive disorders including epilepsy or a history of such disorders. [There is a potential risk of decreasing a seizure threshold.]

(4) Patients with a history of suicide attempt or suicidal thoughts (the symptom may be aggravated).

(5) Elderly patients [See "Administration to the Elderly."]

2. Important Precautions

(1) Seroquel may cause **orthostatic hypotension especially at the early stage of treatment.** If hypotensive symptoms, such as **dizziness and dizziness at standing**, occur, appropriate actions should be taken, for example reduce the dose.

(2) Since Seroquel primarily acts on the central nervous system, it may cause **sleepiness, decreases in attentiveness, concentration and reflexive movements, etc.** Therefore, patients should be advised not to **drive or operate hazardous machinery** when taking the drug.

(3) Since **psychiatric symptoms may be aggravated** when the treatment is switched from the previous medication, while the patients should be carefully monitored, it is desirable to **gradually increase the dosage of this product** as well as reducing the dosage of the previous medication. In the event that symptoms are aggravated, appropriate measures should be taken such as switching to other therapies.

3. Drug Interactions

(1) **Contraindications for coadministration** (Seroquel should not be coadministered with the following drugs.)

Name of Concomitant Drug	Signs and Symptoms, and Treatment for them	Mechanism of Action and Risk Factor
Epinephrine Bosmin	Since the effects of epinephrine are reversed, serious blood pressure decreased may occur.	Epinephrine is adrenergic α, β-receptor agonist. Since α-receptor is blocked by this product, agonist effects on β-receptor become superior, and blood pressure decreasing effect is enhanced.

(2) **Precautions for concomitant use** (be administered with care when concomitantly used with the following drugs.)

Name of Concomitant Drug	Signs and Symptoms, and Treatment for them	Mechanism of Action and Risk Factor
Central nervous system depressants, Alcohol	As the effects of CNS depression may increase, quetiapine should be given with care, paying attention to the clinical response and tolerability of the individual patient.	Pharmacodynamic interactions may occur.
CYP3A4 inducers including phenytoin, carbamazepine, barbiturates or rifampicin*	The effects of quetiapine may decrease.	Quetiapine clearance may be increased as a result of induction of CYP3A4, which is the primary enzyme responsible for metabolism of quetiapine. In the foreign subjects given quetiapine and phenytoin concomitantly, oral clearance of quetiapine increased 5 times and Cmax and AUC of quetiapine decreased by 66% and 80%, respectively.
Thioridazine*	The effects of quetiapine may decrease.	Following concomitant use with

		thioridazine, oral clearance of quetiapine increased 1.7 times and Cmax and AUC of quetiapine decreased by 40-50%.
CYP3A4 inhibitors including erythromycin	As the effects of quetiapine may increase, quetiapine should be given with care, paying attention to the clinical response and tolerability of the individual patient.	Quetiapine clearance may decrease as a result of non-competitive inhibition of CYP3A4, which is the primary enzyme responsible for metabolism of quetiapine. It has been reported that plasma concentrations of this drug increased in the foreign patients who were co-administered with ketoconazole.

*The dose of Seroquel may need to be reduced if these drugs are withdrawn or replaced with a non-inducer of CY3A4.

4. Adverse Reactions

<Japanese clinical studies>

Adverse reactions including laboratory data abnormalities were observed in 365 patients (62.5 %) out of 584 Japanese patients who were evaluated for adverse reactions. Major findings were insomnia (19.3%), nervousness (17.8%), somnolence (14.2%) malaise (10.8%) and anxiety (10.6%). Abnormal changes in laboratory test values included ALT (GPT) increased (8.3%), CK (CPK) increased (7.4%), T4 decreased (7.1%), AST (GOT) increased (6.6%), prolactin increased (6.3%) and LDH increased (5.5%). (Accumulation of data until the approval submission: December 2000)

<Western long term study>

Of 469 evaluable patients for the safety evaluation in total, adverse drug reactions including abnormal changes in laboratory test values were reported in 149 patients (31.8%). The major adverse rug reactions were somnolence (6.2%), hypotension postural (5.1%), etc.

(1) Clinically Significant Adverse Reactions

1) **Syndrome malin** (0.2%): If akinetic mutism, severe muscle rigidity, deglutition difficulty, tachycardia, blood pressure fluctuation, perspiration, etc., occur and following that pyrexia occurs, discontinue administration. Carry out appropriate treatments as well as systematic management such as cooling body and supplying water. When syndrome malin occurs, often increased leukocyte or elevated serum CPK are observed, and decrease in kidney function accompanying myoglobinuria may be observed.
2) **Tardive dyskinesia** (0.9%): In a long term administration, sometimes involuntary movement of mouth, etc. may occur and may continue after the discontinuation of the treatment.

(2) Other Adverse Reactions

1) Adverse reactions from Japanese clinical studies

	Not less than 5% or incidence unknown	Less than 5% and not less than 0.1%
Psychoneurotic	Insomnia, anxiety, nervousness, somnolence, headache, dizziness	Manifestation of hallucination, convulsion, amnesia, aggressive reaction, stupor, neurosis, manifestation of delusion, increased libido, emotional lability, agitation, confusion, abnormal thought, suicide attempt, personality disorder, manic reaction, euphoria, choreoathetosis, migraine, nightmare, depressive reaction, soliloquy, impulsive behaviour, automatism
Extrapyramidal syndrome[2)]	Akathisia, tremor, dyslalia	Muscle rigidity, salivation, bradykinesia, gait abnormality, dyskinesia, dysphagia, dystonia, oculogyric crises
Hematologic		Granulocytopenia
Cardiovascular	Tachycardia	Hypotension postural, palpitation, hypotension, hypertension, bradycardia, arrhythmia, syncope, electrocardiogram abnormal
Hepatic	AST (GOT) increased, ALT (GPT) increased, LDH increased	AL-p increased, γ-GTP increased, bilirubinemia
Respiratory		Sputum expectoration difficult, rhinitis
Gastrointestinal	Constipation, anorexia,	Increased appetite, nausea, vomiting, abdominal pain, diarrhoea, ileus, dyspepsia
Eye		Disorder of pupillary reflex
****Endocrine**	Hyperprolactinemia T4 decreased, Hyperglycaemia [1)]	Abnormal menstruation, thyroid disorder, hypercholesterolaemia, hyperlipaemia
* **Hypersensitivity**		Rash
Urinary		Micturition disorder, dysuria, urinary incontinence, urinary retention, BUN increased
Miscellaneous	Malaise, adynamia, CK (CPK) increased	Dry mouth, sweating increased, pyrexia, weight gain, weight loss, chest pain, muscle pain, hyperkalemia, tongue paralysis, hypoaesthesia, back pain, obesity, oedema, hot flush, tooth pain

**1): The incidence is unknown because the adverse drug reactions have been reported spontaneous AEs which are not reported in the Japanese clinical studies.

2): Data collected based on the commonly used terms.

2) Adverse reactions from Western long term study used for the submission (469 cases).

	Not less than 5% or frequency	0.1 to less than 5%

	unknown	
Psychoneurotic	Somnolence	Insomnia, nervousness, anxiety, headache, convulsion, amnesia, agitation, dizziness, confusion, abnormal thought, suicide attempt, manic reaction, nightmare, depression, schizophrenic reaction, incoordination, delirium, aggressive reaction
Extrapyramidal syndrome[2)]		Akathisia, tremor, muscle rigidity, dyslalia, dystonia, dyskinesia, oculogyric crisis, active motor retarded, salivation
****Hematologic**	Eosinophilia [1)]	Leukopenia, anaemia
Cardiovascular	Hypotension postural	Tachycardia, palpitation, hypotension, hypertension, bradycardia, vasodilation
Hepatic		AST (GOT) increased, ALT (GPT) increased, Al-p increased
Respiratory		Cough increased
Gastrointestinal		Constipation, increased appetite, nausea, vomiting, diarrhoea, dyspepsia, flatulence, gastritis, digestive tract disorder, haematemesis, rectum disorder, abdominal pain
Eye		Amblyopia, conjunctivitis
Endocrine		Thyroid disorder, abnormal menstruation, T3 increased
****,* Hypersensitivity**	Angioedem [1)]	Rash, itchiness
****Urinary**	Priapism [1)]	Ejaculation abnormality, impotence, micturition disorder
***Miscellaneous**		Dry mouth, perspiration, adynamia, weight gain, weight loss, chest pain, CK (CPK) increased, muscle pain, back pain, facial oedema, neck rigidity, peripheral oedema, phyma, overdose, pelvic pain, tooth disorder, gout, arthralgia, arthrosis, bursitis, myasthenia, spasm generalized, deterioration reaction, accidental injury, ear disorder, taste perversion, fever, acne

**1): The incidence is unknown because the adverse drug reactions specified in Core Data Sheet which are not reported in the Western long term study.

2): Data collected based on the commonly used terms.

5. Administration to the Elderly

In the elderly, the oral clearance of quetiapine was 30-50% lower and the AUC was 1.5 times higher than those in the non-elderly and a tendency towards persistently elevated blood concentrations was reported. The treatment should thus be started with a small dose, such as 25mg of quetiapine a day, and then the dose should be gradually increased in increments of 25-50mg/day to an effective dose, depending on the response and tolerability in each patient. (See

"PHARMACOKINETICS".) The tendency that incidence of hypotension postural increases compared with the non-elderly, was reported in the Western clinical studies.

6. Administration to Pregnant and Nursing Women

(1) Pregnant women etc.: This drug should be given to pregnant or possibly pregnant women only if the expected therapeutic benefits outweigh the potential risk associated with treatment. [The safety of quetiapine has not been established in pregnancy. Animal studies (in rats and rabbits) have shown that the drug is excreted into fetus.]

(2) Nursing women etc.: If this drug is used in lactating women, breast feeding must be discontinued during treatment. [An animal study (in rats) has shown that quetiapine is excreted in breast milk.]

7. Administration to Children etc.

The safety of this drug in children etc. has not been established (lack of clinical experience).

8. Overdose

Signs and symptoms: The common symptoms are somnolence and sedation, palpitation, hypotension, etc.

Treatment: As there is no specific antidote to quetiapine, maintenance therapies should be carried out. Gastric lavage at an early stage is effective. If respiratory suppression is seen, appropriate actions such as maintaining a patent airway and artificial ventilation should be carried out.

9. Caution for Application

At dispensation: Instruct the patient that the tablets in PTP pack should be taken out of the PTP sheet before swallowing. [It was reported that, due to taking a piece of a PTP sheet by mistake, a sharp corner of the sheet pieced tunica mucosa esophagi and then caused perforation, resulted in a serious complication such as mediastinitis.]

10. Other cautions

(1) Sudden death from an unknown cause was reported during the treatment with this product.

(2) Myocardial infarction and gastric ulcer haemorrhagic of which the causality with this product is unknown were reported in the Japanese clinical studies. Acute renal failure was reported in the Western long term study used for the submission.

(3) When dogs were orally given high-dose of quetiapine (100mg/kg/day for 6 months and 12 months), some showed posterior triangular cataract, which was considered to be caused by inhibition of cholesterol biosynthesis. However, no cataract was observed in cynomolgus monkeys (up to 225mg/kg/day for 56 weeks) or rodents. In clinical studies, no drug-related corneal opacities have been observed.

(4) When this product was orally given to rats for 24 months in the carcinogenicity study, the increased incidence of mammary tumour was reported in female rats in the 20mg/kg/day or

higher treatment groups. Although it is reported that these tumour findings are related to prolactin[1] in rodents, the relationship between increased concentrations of prolactin and oncogenesis is not clarified in human.

[PHARMACOKINETICS]

1. Blood concentrations

(1) Schizophrenic patients were given quetiapine orally twice a day repeatedly which was increased by 25 to 100mg per dose. Figure 1 and Table 1 show the time course of plasma quetiapine concentrations and the pharmacokinetic parameters, respectively, after the 7th dose at 100mg[2].

The plasma quetiatpine concentration reached its peak (mean: 397ng/mL) at 2.6 hours after administration in the non-elderly. Quetiapine was then eliminated swiftly from plasma with a half-life of 3.5 hours. The plasma concentrations in the elderly were higher than those in the non-elderly. The $AUC_{0\text{-}12h}$ in the elderly (mean: 2.59μg·h/mL) was about 1.5 times higher than that in the non-elderly (mean: 1.69μg·h/mL).

Figure 1: Time course of the plasma quetiapine concentrations following twice daily repeated administration of quetiapine (100mg) to schizophrenic patients (mean±SE, 12 non-elderly and 11elderly patients)

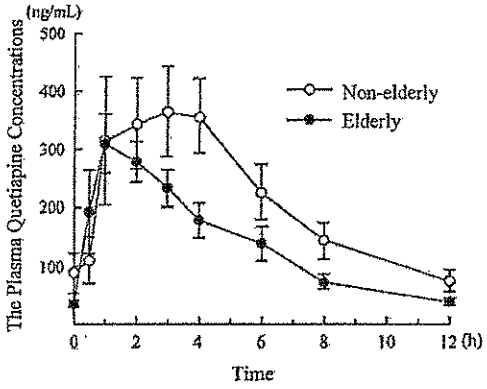


Table 1: Pharmacokinetic parameters following twice daily repeated administration of quetiapine (100mg) to schizophrenic patients (mean±SE)

Group	n	Cmax (ng/mL)	Tmax (h)	$AUC_{0\text{-}12h}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/f (L/h)
Non-elderly	12	397±57	2.6±0.7	1.69±0.19	3.5±0.2	67.1±7.1
Elderly	11	483±96	2.9±0.3	2.59±0.54	3.6±0.3	50.9±6.7

(2) Western schizophrenic patients were given quetiapine orally three times a day repeatedly, which was increased by 25 to 250mg per dose. Table 2 shows pharmacokinetic parameters at the steady state after 75mg, 150mg or 250mg quetiapine administration. The plasma quetiapine concentrations increased in a dose-dependent manner with no gender difference.

Table 2: Pharmacokinetic parameters of quetiapine at steady-state after repeated administration of quetiapine TID to western schizophrenic patients (Mean±SE, n=11 to 13)

Dose	Sex	Cmax (ng/mL)	Tmax (h) [a]	$AUC_{0\text{-}8h}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/f (L/h)
75 mg tid	Male	277± 54	1.0 (0.5-3.0)	1.07±0.19	2.7±0.1 [b]	89±12
	Female	294± 41	1.0 (0.5-3.0)	1.20±0.17	3.4±0.3 [b]	86±16
150 mg tid	Male	625±121	1.0 (0.5-4.0)	2.30±0.33	3.0±0.3 [b]	78±10
	Female	572± 63	1.5 (0.5-4.0)	2.41±0.34	4.4±0.8 [b]	73±8
250 mg tid	Male	778±108	1.5 (0.5-4.0)	3.38±0.46	5.8±0.3 [c]	87±10
	Female	879± 72	1.5 (1.0-3.0)	4.08±0.53	6.6±0.8 [c]	72±9

a) Median (range), b) Half-life at 3-8 hours after dosing, c) Half-life in the terminal phase

2. Effects of hepatic impairment (data in foreign population) [3]

Following single oral administration of 25mg quetiapine to patients with hepatic impairment (alcoholic cirrhosis), Cmax and $AUC_{0\text{-}8h}$ of quetiatpine were (about 1.5 times) higher and $t_{1/2}$ was (about 1.8 times) longer in these patients compared with in healthy subjects.

Table 3: Pharmacokinetic parameters following single oral administration of 25mg quetiapine to western patients with hepatic impairment (mean±SE, n=8)

Subjects	Cmax (ng/mL)	Tmax (h) [a]	$AUC_{0\text{-}\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/f (L/h)
Patients with hepatic impairment	78.5±14.4	1.0 (0.5 - 1.5)	0.386±0.077	5.5±1.0	79.4±10.7
Healthy subjects	53.0± 3.5	1.25 (0.6 - 3.0)	0.248±0.020	3.1±0.2	105±8

a) Median (range)

3. Absorption and effects of food

Quetiapine administered orally was well absorbed. There was no effect of food on Cmax or AUC of quetiapine.

4. Protein binding [4]

The percent binding of quetiapine to human plasma proteins was 83.0%.

5. Metabolism [5]

(1) Quetiapine was extensively metabolised via multiple pathways. The primary P450 enzyme involved in metabolism of quetiapine was CYP3A4.

(2) The main metabolites in human plasma did not have significant pharmacological activity.

(3) In an *in vitro* study, quetiapine and its several metabolites showed weak inhibitory effects on CYP1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10-fold higher than plasma quetiapine concentrations observed in humans. These results did not suggest occurrence of drug interactions.

6. Excretion [6] [7]

(1) Following single oral administration of 20mg quetiapine to healthy adult males, the urinary excretion of the parent compound was less than 1% of the dose.

(2) Following administration of ^{14}C-labelled quetiapine to foreign schizophrenic patients, 72.8% and 20.2% of the radioactivity were excreted in urine and feces, respectively. The parent compound in urine and feces accounted for less than 1% of the total radioactivity.

[CLINICAL EXPERIENCE]

In clinical trials in 556 patients implemented in Japan, which include two double blind comparative studies, the improvement rate of final overall improvement ratings has proved that Seroquel is effective in the treatment of schizophrenia. The followings are the results:

1. In clinical trials in 553 patients with schizophrenia, improvement rates as "marked improvement + moderate improvement" were 42% (232/553). The two double blind comparative studies showed usefulness of Seroquel on schizophrenia. [8)9)]
2. In an open study in treatment resistant patients, Seroquel showed an improvement rate of 40.9 % (9/22), indicating the efficacy in this group of patients. [10)]

Overseas clinical trials have demonstrated that Seroquel is effective when given twice daily. This is further supported by the data from a positron emission tomography (PET) study in schizophrenic patients in the West. It identified that for quetiapine, $5HT_2$ and D_2 receptor occupancy, which is important in manifestation of the effect, is maintained for up to 12 hours.[11)]

[PHARMACOLOGY]

1. Pharmacological Actions

(1) Affinity to receptors

In *in vitro* studies with rat brain tissues, quetiapine exhibited affinities at dopamine D_1, dopamine D_2, serotonin $5HT_1$ and $5HT_2$, histamine H_1, adrenaline α_1 and adrenaline α_2 receptors, but exhibited almost no affinities at muscarine and benzodiazepine receptors. Affinity at serotonin $5HT_2$ receptors was higher than affinity at dopamine D_2[12)].

(2) Dopamine and serotonin receptor antagonism

Quetiapine dose-dependently suppressed reactions induced by a dopamine agonist, apomorphine, such as blinking in squirrel monkeys and cage climbing and swimming difficulty in mice[12)]. It also dose-dependently suppressed head twitching induced by a serotonin agonist, quipazine, in rats[13)].

(3) Effect of quetiapine on extrapyramidal system

Quetiapine had a lower liability to induce dystonia in monkeys and to induce catalepsy in rats than haloperidol. Electrophysiological studies in rats demonstrated that quetiapine selectively affected limbic but not nigrostriatum that might be closely related to EPS[12)]. In placebo controlled double blind comparative studies in schizophrenic patients in the

West, the incidence of extrapyramidal disorders did not show significant difference from the placebo group.

(4) Effect on plasma prolactin level
Unlike haloperidol, quetiapine did not cause sustained elevation in plasma prolactin level in rats[12]. In the Western placebo-controlled double-blind comparative studies in schizophrenic patients, the prolactin level did not show significant difference from placebo group.

2. Mechanism of Action[12]

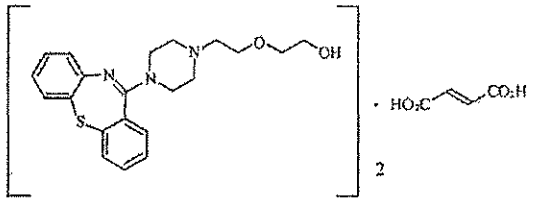
The pharmacological characteristics of Seroquel are the higher affinity at serotonin $5HT_2$ receptors compared with the affinity at dopamin D_2 receptors and the affinity to various receptors. These are thought to contribute to Seroquel's clinical effect.

[PHYSICOCHEMICAL DESCRIPTION]

Generic Name: Quetiapine fumarate (JAN)
(WHO recommended INN: quetiapine)

Chemical Name: bis {2-[2-(4-dibenzo [*b*, *f*][1, 4] thiazepin-11-yl-1-piperazinyl) ethoxy] ethanol} monofumarate

Structural Formula:



Molecular Formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$

Molecular Weight: 883.10

Melting point: 174°C (decomposition)

Partition coefficient: 0.35 (pH3.0, 1-octanol/buffer solution)
30.85 (pH5.0, 1-octanol/buffer solution)
389.70 (pH7.0, 1-octanol/buffer solution)

Description: Quetiapine fumarate is a white powder. Quetiapine fumarate is soluble in dimethylformamide, sparingly soluble in methanol, slightly soluble in ethanol or water and very slightly soluble in acetonitrile or diethylether.

[PACKAGING]

Seroquel 25 mg tablets: 100 tablets (10 tablets×10),
500 tablets (10 tablets×50), 1000 tablets (bottle)
Seroquel 100 mg tablets: 100 tablets (10 tablets×10),
500 tablets (10 tablets×50), 1000 tablets (bottle)

[MAJOR REFERENCES]

1) B Vonderhaar: Pharmacol. Ther., 79 : 169-178, 1998
2) In-house report
3) In-house report
4) In-house report
5) In-house report
6) Murasaki M et al: Clinical Evaluation 27: 101, 1999
7) In-house report
8) *Murasaki M et al: Japanese Journal of Clinical Psychopharmacology 4 (1); 127, 2001
9) *Kudo Y et al: :Japanese Journal of Clinical Iyaku 16 (12); 1807, 2000
10) Maeda H et al: Japanese Journal of Clinical Psychopharmacology 2(6); 653, 1999
11) Gefvert O et al.: Psychopharmacology 135; 119, 1998
12) J.M.Goldstein : Schizophrenia : Breaking Down the Barriers. Edited by S.G.Holliday et al., John Wiley & Sons Ltd, 1996
13) In-house report

[REQUEST ADDRESS]

Fujisawa Pharmaceutical Co. Ltd. The 1st PMS department
1-6, 2-chome, Kashima, Yodogawa-ku, Osaka, 532-8514, Japan
TEL: 06-6201-4312

Sold by: Fujisawa Pharmaceutical Co., Ltd.
3-4-7 Doshomachi, Chuo-ku, Osaka
Manufactured by: AstraZeneca Ltd.
1-1-88 Oyodonaka, Kita-ku, Osaka

English Tanslation

November 7, 2002

Emergency Safety Information on
Diabetic Ketoacidosis and Diabetic Coma due to an Increase in Blood Glucose Level during Administration of Seroquel, Antipsycotic

AstraZeneca K.K. (Head Office: Kita-ku, Osaka, President: Martin Wright) today issues Emergency Safety Information (ESI) on diabetic ketoacidosis and diabetic coma due to an increase in blood glucose level during administration of Seroquel 25mg, 100mg tablets (quetiapine fumarate).

Since Seroquel was launched in Japan in February 2001, hyperglycemia was added under the section "Precautions for Use: Other Adverse Reactions" of our prescribing information in July 2002 based on the three hyperglycemia cases accumulated by that time. Until now, a total of 13 cases, including one death case, were accumulated concerning hyperglycemia, diabetic ketoacidosis and diabetic coma which developed during administration of Seroquel. Upon MHLW's instruction, we have immediately taken steps to call for attention more thoroughly by issuing the ESI.

In Japan, AstraZeneca developed, obtained approval and is manufacturing Seroquel, but Fujisawa Pharmaceutical Co., Ltd. is marketing the product. AstraZeneca is responsible for evaluating adverse events and reporting them to the MHLW, while Fujisawa is in charge of collecting safety information based on a GPMSP agreement between the two companies. Thus, Fujisawa will be distributing the ESI.

Seroquel is an atypical antipsychotic which controls schizophrenia. It is effective for negative symptoms of schizophrenia for which conventional typical antipsychotics do not show adequate therapeutic effect. Also it has fewer side effects of extrapyramidal syndrome (EPS) such as parkinsonism, akathisia, dyskinesia, dystonia. We consider that Seroquel has proven safety and efficacy with over 4 million patient exposures worldwide in 78 countries. We at AstraZeneca think that there is no evidence to conclude that Seroquel directly causes these diabetes related conditions and we will continue to investigate and evaluate concerning this point. The incidence rate of events reported is less than 0.01% world-wide.

As Seroquel improves both positive and negative symptoms of schizophrenia, and has fewer EPS side effects treatment can be continued after the patient leaves hospital. Also, we think Seroquel is useful as it helps enhance QOL of the patients and increases the chance for the patients to go back to social life. For Seroquel to continue to contribute to the patients with schisophrenia, it must be properly understood and used. We expect that this Emergency Safety Information will promote proper understanding and use of Seroquel, thereby maximizing the benefits of the patients.

Attachment: Glossary on symptoms and adverse events (no translation)

Inquiries to Fumiko Muramoto
090-8655-8277/06-6453-7848

Draft

Voicemail Script for: Lisa Lloyd-Washington, Brand Director, SEROQUEL

Audience: Hospital, Long Term Care, & Specialty Care Sales Teams

Send: **RESERVE - November 6, 2002**

Hello, this is Lisa Lloyd-Washington, Brand Director for SEROQUEL and this message is going to Linda Palczuk, Nick Harsh, Mark Page and the 3 Areas Sales Directors. Please cascade this message to the RSD's, DSM's, PSS's, MIS's and Account Directors.

I would like to notify you of a situation that you may be asked about from your customers. The MHLW (Regulatory Authority in Japan) has imposed changes to the label for Seroquel in Japan to include a contraindication regarding the use of Seroquel in patients with diabetes or a history of diabetes. In addition, there has also been a warning statement added which includes a monitoring requirement for blood glucose (in all patients). MHLW imposed this label change following **very rare** reports of diabetic coma, diabetic ketoacidosis, or diabetic-related fatalities coincident with the use of Seroquel. As was the case for Lilly when these changes were required for the Zyprexa label back in April of this year, AstraZeneca will also be required to issue a "Dear Healthcare Provider" Letter in Japan, notifying the medical community of these changes to the label.

So, what does this mean for us in the U.S.? Based on current safety data on the use of Seroquel in this patient group, we consider the need for any further label changes unlikely (including in the US), since there is **no causal relationship established between** Seroquel and diabetes-related conditions. Also, please remember that AstraZeneca's Core Data Sheet does not contain statements, contraindications, or warnings relating to diabetes mellitus; however, our US label has always had diabetes mellitus listed in the "Adverse Events" Section.

It is important to place this label change in Japan into perspective. First, the change was requested based on **very rare** reports of diabetes-related conditions (an incidence rate of less than 0.01% world-wide). In many of these reports other factors caused or contributed to these events, such as not taking the medicine prescribed for diabetes, drinking large volumes of sweetened beverages, not adhering to the appropriate diabetes diet, or complications of other medical conditions. In the remaining reports there was **insufficient information** provided to establish a causal relationship with the administration of SEROQUEL.

AstraZeneca maintains a robust clinical safety database and has fulfilled every compliance requirement, meeting reporting obligations to all regulatory authorities, including the FDA. We conscientiously monitor adverse events reported in worldwide clinical use, and investigate all serious adverse events promptly. We continuously measure factors in our ongoing clinical trial programs and we have already incorporated these measures into trials that will be reading out in the near future. We anticipate that

this data will further support the excellent safety and tolerability profile of Seroquel that physicians have come to trust.

At this point in time, we are just giving you this notice for information only so that you are aware if the topic is raised. It is imperative that you do not proactively discuss this issue with your customers. You will receive further guidance in the future on how to address this issue. Until then, please communicate these 2 points if you are asked about the change in the SEROQUEL label in Japan:

- SEROQUEL has proven safety and efficacy – with over 4 million patient exposures to SEROQUEL worldwide.
- There is **no causal relationship established between** Seroquel and diabetes-related conditions.

While this is obviously disappointing news, it is important that we do not let this notification become a distraction. We must continue to focus on selling the features and benefits of SEROQUEL, utilizing the Well! Accepted! message.

I wish you continued good selling!

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

November 2002

NO. 02-5

Dear Dr. Letter

Diabetic ketoacidosis and diabetic coma due to an increase in blood glucose level during administration of Seroquel® 25mg, 100mg tablets (quetiapine), an antipsychotic drug

Since February 2001 when Seroquel was started to be marketed, 12 serious cases (including 1 death) of hyperglycaemia, diabetic ketoacidosis, and diabetic coma where causality with the drug could not be ruled out have been reported (estimated number of patients who used Seroquel of the end of September 2002 was approximately 130,000). Hyperglycaemia was added in the "Precautions for use" to call attention in July 2002; however, based on the discussion of serious cases, "Contraindication" and "Precautions for use" were revised, and "Warning" was added to the package leaflet. This drug should be cautiously administered with strict attention to the following instructions. If Adverse reaction as above is confirmed, please contact the person in charge of Drug Information of Fujisawa which is the marketing company for Japan.

Manufacturing company: AstraZeneca K.K.
Marketing company: Fujisawa Pharmaceutical Co. Ltd.

1. **Seroquel must not be administered to patients with diabetes or a history of diabetes.**

In diabetic patients or patients having a history of diabetes, blood glucose levels may elevate, which may rapidly aggravate metabolic conditions. This drug must not be given to such patients.

2. **During administration of Seroquel, the patient should be monitored carefully including measurement of blood glucose levels.**

During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration of the drug may cause serious adverse reactions such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.

3. **Information on the adverse reactions and action to be taken must be fully explained to the patient and the family.**

Prior to administration of the drug, sufficient explanation should be provided to the patient and the family that significant adverse reactions including diabetic ketoacidosis and diabetic coma may occur. They should be instructed to stop administration of the drug and visit hospital if any symptoms such as thirst, polydipsia, polyuria, increased urinary frequency or others appear.

"Warning", "Contraindication" and "Precautions for use" were revised on the underside of the leaflet.

Contact : Post-Marketing Surveillance 1, Fujisawa Pharmaceutical Co., LTD.
1-6, Kashima 2-Chome, Yodogawa-ku, Osaka, Japan, 532-8514
Phone: +81-6-6390-5266
Fax: +81-6-6304-1319

(Narratives)
Not fixed

No.	Sex, age, reason for use [Complication]	Clinical course and treatment
1		
	Concomitant drugs:	
2		
	Concomitant drugs:	
3		
	Concomitant drugs:	
4		
	Concomitant drugs:	

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

Dear Dr. Letter

"Warning", "Contraindication" and "Precautions for use"

"Warning", "Contraindication" and "Precautions for use" were revised as follows. This revision is based on the post-marketing incidence of hyperglycaemia.

[Warning]

1. During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration may cause significant side effects such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.
2. Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency and also instructed to stop administration of the drug and visit hospital if any of these symptoms appear. [See "Important basic precautions"]

[Contraindication] The drug must not be given to the following patients.

5. Patients with diabetes or a history of diabetes

[Precautions for use]

1. Careful administration (The drug should be given with particular caution in the following patients.)

(6) Patients with a family history of diabetes, or those having diabetes risk factors such as hyperglycaemia or obesity [See "Important basic precautions"]

2. Important basic precautions

(1) Administration of the drug may markedly increase blood glucose, in some patients, leading to life-threatening clinical courses including diabetic ketoacidosis or

diabetic coma. During administration of the drug, blood glucose levels should be measured, and thirst, polydipsia, polyuria, increased urinary frequency and others should be fully monitored. Especially for the patients with diabetes risk factors such as hyperglycaemia or obesity, increased blood glucose may rapidly aggravate metabolic conditions.

(2) Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above serious side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency, and also instructed to stop administration of the drug if such a symptom may appear, and visit hospital.

(3) Administration of the drug may increase body weight. Pay attention to obesity, and if a sign of obesity is observed, appropriate action including diet therapy or exercise therapy should be taken.

3. Adverse Reactions

(1) Clinically significant adverse reactions

1) Hyperglycaemia, diabetic ketoacidosis, and diabetic coma: Hyperglycaemia may appear, and occurrence of diabetic ketoacidosis or diabetic coma may lead to life-threatening clinical courses. Measurement of blood glucose and observation of thirst, polydipsia, polyuria, and increased urinary frequency should be fully carried out. If any abnormalities are found, administration should be stopped, and appropriate action such as administration of insulin preparations should be taken.

(Only revised parts are described.)

Seroquel - Diabetes Q&A

Key Messages

- **Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.**
- **There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes.**
- **There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.**

Q: Is glucose dysregulation an issue with Seroquel?

- There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes. There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.

- **If pushed and asked specific questions about diabetic comas, diabetic ketoacidosis, or fatalities associated with Seroquel:**
  - There have been over 4 million patient exposures to Seroquel worldwide. There have been **very rare** reports of diabetic coma, diabetic ketoacidosis, or diabetic-related fatalities **coincident** with the use of Seroquel (incidence rate is <0.01% - qualifying for a very rare classification, defined by the CIOMS III Working Group, 1995: "Allocation of Frequency Descriptors to Adverse Drug Reactions").
  - In many of these reports, *other factors* caused or contributed to these events, such as not taking the medicine prescribed for diabetes, drinking large volumes of sweetened beverages, not adhering to the appropriate diabetes diet, or complications of other medical conditions. In the remaining reports there was insufficient information provided to establish a causal relationship.
  - There is no evidence of a causal relationship between Seroquel and these events.

Q: What are the label changes that the MHLW has imposed on Seroquel in Japan?

- The MHLW has imposed changes to the JPI for Seroquel in Japan to include a **contraindication** regarding the use of Seroquel in patients with diabetes or a history of diabetes. In addition there has also been a **warning statement** added which includes a monitoring requirement for blood glucose (in all patients).

Q:Why has the MHLW imposed a restricted label on Seroquel in Japan?

- MHLW imposed this label change following **very rare** reports of diabetic coma, diabetic ketoacidosis, or diabetic-related fatalities **coincident** with the use of Seroquel.
- In many of these reports *other factors* caused or contributed to these events, such as not taking the medicine prescribed for diabetes, drinking large volumes of sweetened beverages, not adhering to the appropriate diabetes diet, or complications of other medical conditions. In the remaining reports there was insufficient information provided to establish a causal relationship.
- There have been over 4 million patient exposures to Seroquel worldwide.
- There is no evidence that Seroquel causes diabetes or worsens diabetes.

Q: Do any other atypicals have such a restriction to the label?

- Olanzapine has similar chages to the label made in April

Q: Do you anticipate a requirement to change the Seroquel label in other countries?

- Based on current safety data on the use of Seroquel in this patient group, we do not anticipate the need for any label changes, since there is no evidence that Seroquel causes diabetes or worsens diabetes (AstraZeneca's Core Data Sheet does not contain statements, contraindications, or warnings relating to diabetes mellitus). We do not anticipate further Health Authority impositions.

Q: Is glucose dysregulation a class effect?

- There is no evidence to conclude that glucose dysregulation is a class effect of atypical antipsychotics.
- There is no evidence to conclude that glucose dysregulation is caused by Seroquel.

- There is no evidence to conclude that Seroquel causes diabetes or worsens diabetes.

Q: So you have no concerns about this issue?

- The safety or our products is always a high priority for AstraZeneca.
- AstraZeneca maintains high ethical standards and through our global safety database we continuously monitor all our products, including Seroquel, and keep health authorities updated.
- AstraZeneca maintains a robust clinical safety database and has fulfilled every compliance requirement, meeting reporting obligations to all regulatory authorities, including MHLW and FDA.
- Through our global safety database we continuously monitor all our products, including Seroquel, and review this information (to keep the company Core Data Sheet current) and to update Health Authorities accordingly.

Q: Are you carrying out additional work in this area to ensure that Seroquel does not have a problem with glucose dysregulation?

- We conscientiously monitor adverse events reported in worldwide clinical use, and investigate all serious adverse events promptly.
- We continuously measure factors in our ongoing clinical trial programmes.
- Data from these sources support the excellent safety/tolerability profile of Seroquel.
- AstraZeneca investigates thoroughly to obtain additional information from physicians who report adverse events, in order to understand the issues as fully as possible.

Q: Does Seroquel have a direct effect in causing diabetes?
Q: Does Seroquel aggravate diabetes?
Q: Is there an increased risk of new onset diabetes or new onset diabetes with Seroquel?

- There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes. There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.

Q: How big is the risk of patients suffering from diabetes whilst on Seroquel?

- There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes. There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.
  - There is no evidence of a causal relationship between Seroquel and these events.
  - There have been over 4 million patient exposures to Seroquel worldwide. There have been **very rare** reports of diabetic coma, diabetic ketoacidosis, or diabetic-related fatalities **coincident** with the use of Seroquel. In many of these reports, *other fact*ors caused or contributed to these events, such as not taking the medicine prescribed for diabetes, drinking large volumes of sweetened beverages, not adhering to the appropriate diabetes diet, or complications of other medical conditions. In the remaining reports there was insufficient information provided to establish a causal relationship.

Q: Is the incidence *rate* of these reports greater in Japan than ROW – i.e. a difference in sensitivity in Japanese patients?

- There is no evidence to suggest that Japanese patients are at higher risk than elsewhere in the world.
  [For background: Incidence of diabetes may vary by country; Reference: Williams Textbook of Endocrinology, 9th ed., 1998].

Q: How does the background incidence of diabetes in schizophrenia patients compare with the general population?

- The prevalence of diabetes in schizophrenic patients is higher than in the general population.[1]
  - One US study showed the prevalence of diabetes in schizophrenic patients ranged from 9 to 14%.[2] This compares to a prevalence of 6% in the general US population.[3] Another study in Italy showed a prevalence of diabetes in schizophrenic patients of 15.8%.[4] This compares with a prevalence of 3% in adults > 18 years old In Italy.

References:

1 Meltzer HY. Putting metabolic side effects into perspective: Risks versus benefits of atypical antipsychotics. Journal of Clinical Psychiatry, 62 Suppl 27: 35-9, 2001

2 Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, and Lehman A. Prevalence and Correlates of Diabetes in National Schizophrenic Samples. Schizophrenia Bulletin 26 (4): 903-912, 2000.

3 Powers AC, Chapter 33: Diabetes Mellitus, in Harrisons' Principles of Internal Medicine, 15th ed, 2109-2137, 2001.

4 Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL. Diabetes Mellitus in Schizophrenia Patients. Comprehensive Psychiatry 37(1): 68-73, 1996

Q: How do other regulatory authorities view Seroquel with regard to the diabetes issue?

- A number of other regulatory authorities have imposed some labelling relating to diabetes mellitus, but far less stringent than that imposed by MHLW:
  - US - Seroquel PI has diabetes mellitus listed in the "Adverse Events" Section.
  - EU – the Pharmacovigilance Working Party of the CPMP reviewed the class in June 2001. Seroquel SmPC has language "Special Warnings and Precautions for Use" section stating that hyperglycaemia and exacerbation of preexisting diabetes has been reported in very rare cases and that appropriate clinical monitoring is advisable. Similar wording is also in the Undesirable Effects section.
  - In New Zealand, the label contains hyperglycaemia, diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis, in the Adverse Effects section.
  - –The Italian label includes warnings and precautions that hyperglycaemia and the exacerbation of pre-existing diabetes have been reported rarely, and that monitoring is advisable.
  - In UK, discussions regarding these issues are pending with MCA and should be resolved by the end of the year. -.

Q: Is there an undue risk with administering Seroquel to patients?

- Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.

Q: Is there a need to protect patients outside Japan with similar monitoring measures?

- Seroquel has proven efficacy and safety with over 4 million patient exposures to worldwide.
- There is no evidence of a causal relationship between Seroquel and these events.
- There have been **very rare** reports of diabetic coma, diabetic ketoacidosis, or diabetic-related fatalities **coincident** with the use of

Seroquel. A review of these reports indicates *other factors* caused or contributed to these events, such as not taking the medicine prescribed for diabetes, drinking large volumes of sweetened beverages, not adhering to the appropriate diabetes diet, or complications of other medical conditions.

6 November 2002

medical affairs

Publication Alert

SEROQUEL PUBLICATION ALERT NO: 2002_08

Title: **The effects of Novel Antipsychotics on Glucose and Lipid Levels**

Authors: Wirsching D A, Boyd J A, Meng L R, Ballon J S, Marder S R, Wirsching W C

Journal: J Clinical Pyschiatry 63:10, October 2002

Summary
Retrospective small study (sponsored by both Janssen and AstraZeneca) of 215 patients charts. Glucose and lipid level data from 2.5 years before and after the initiation of the target antipsychotic were included. Conclusion is that some of the atypicals, particularly clozapine and olanzapine have greater adverse effects on glucose and triglyceride levels than others such as risperidone. This paper has been cited on Janssen sponsored sites as evidence that risperidone has a more favourable glucose profile than the other atypicals.

For a full copy of the article please order from GLASS (if in US the journal is available on line on the Wilmington ISLA site)

Comments:

1. The data set for quetiapine in this study is very small at only 13 patients.
2. Patients were on quetiapine for a much shorter time (mean 7.3 months)
3. The glucose and lipid levels were assumed to be fasting (they may not have been).
4. Patients taking quetiapine were excluded from the co-variant analysis due the small sample size (13).
5. Ethnic composition varied between groups (clozapine and quetiapine groups were predominately white compared with the other groups).
6. The data is really just as favourable for quetiapine as it is for risperidone. eg. no patients in the quetiapine group required intervention for glucose and the increases were not significantly different for quetiapine (+9% change) compared to risperidone (+3%) with haloperidol at (+7%), clozapine (+14%), olanzapine (+21%). Using a cut off of 126mg/dl for fasting glucose resulted in 36% of patients on risperidone and 13% on quetiapine developing clinically significant elevations in 'fasting' glucose levels. If the cut off was set at 200mg/dl or random blood glucose then 8% of those on risperidone and 0% on quetiapine had clinically significant elevations in fasting glucose levels.
7. The lipid data for quetiapine was good with significant decreases in LDL, triglycerides, and no change on HDL.

Richard Olbrich
Global Medical Affairs Manager - Seroquel
Product Strategy & Licensing

07/November 2002