# QUETIAPINE; QUETIAPINE FUMARATE

| CAS NUMBER: | 111974-69-7 |
| Originator: | ICI |

Drug’s Patent (Pharmaprojects):
- Launch:
- Synonyms:

**Pipeline:**  
- **PI 1100099** (17.12.1996)
- Applicant: Zeneca Inc
- Expiration Date (probable): 27.03.2006
- Priority Number: GB 8607684 (27.03.1986)
- SPC: Expires in Mar. 2012 in GB, NL, LU, BE, CH.

**Resumo:**
- COMPOSTOS DE TIAZEPINA

**RxList Monograph:**
SEROQUEL® (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is C₄₂H₅₀N₆O₄S₂•C₄H₄O₄ and it has a molecular weight of 883.11 (fumarate salt).

Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow) and 200 mg (white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

**Pharmaprojects Monograph:**

**World Status:** Launched  
**Pharma Status:** Active  
**Synonyms:** FK-949  
ICI-204636  
Seroquel  
Seroquel 50% Fine Granule  
ZD-5077  
ZM-204636  
**Originator:** AstraZeneca (UK) [Launched]  
**Licensee:** Astellas (Japan) [Launched]
ACTIVITY DATA

Therapy: Code Description
N5A1 Neuroleptic
N10A Antidepressant
N9A Dependence treatment

Rte of Admin: Code Description
A-PO Alimentary, po

Pharmacology: Code -- Description
5HT-2-AN -- 5 Hydroxytryptamine 2 antagonist
DOPA-D2-AN -- Dopamine D2 antagonist

Linking: Code Code1 Code2 Code3 Status
N5A1 5HT-2-AN DOPA-D2-AN Launched
N10A 5HT-2-AN DOPA-D2-AN Launched
N9A 5HT-2-AN DOPA-D2-AN Phase II Clinical Trial

Indication: Description -- Status
Schizophrenia -- Launched
Psychosis, bipolar -- Launched
Depression, bipolar -- Launched
Addiction, cocaine -- Phase II Clinical Trial

TARGET DATA: 1813: dopamine receptor D2

Target Data Codes:
1813: DRD2; 1813: D2R; 1813: D2DR; 1813: D2 dopamine receptor

Target Families:
1813: Receptor > GPCR > Dopamine.

PHARMACOKINETICS

Model (Dose)--Parameter--Values--Unit
Human (po)--t1/2--7--hr

CHEMICAL DATA

Origin: Code Description
CH-SY Chemical, synthetic

New Entity: Yes
CAS Reg. No: 111974-69-7
111974-72-2
Rot. Bonds: 7
Mol. Formula: C25H29N3O6S
Hydrogen Bond Donors: 1 Hydrogen Bond Acceptors: 5
Mol. Weight: 383.51 AlogP: 2.84
Chemical Name: Ethanol, 2-(2-(4-dibenzo(b,f)(1,4)thiazepin-11-yl-1-piperazinyl)ethoxy)-, (E)-2-butenedioate (2:1) (salt) (CAS)

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**RATING:**
- Novelty: 6 (Leading Compound)
- Development Speed: 4 (Faster than Average)
- Market Size: 4 (US$ 5001-10000 million)
- Total Rating: 14 (Total Rating)

**TEXT:**
Quetiapine fumarate is an atypical antipsychotic agent, developed by AstraZeneca (Company communication, AstraZeneca, Jul 1992; Analysts' Meet, Jul 1986). Treatment-emergent signs include mild-to-moderate insomnia, sedation and transient intermittent sinus tachycardia (17th CINP (Kyoto), 1990, Abs 0-13-3-8; Scrip, 1992, 1778, 15). It does not cause dose-related increases of extrapyramidal symptoms (EPS) in schizophrenia patients. This may be associated with increased patient compliance (Press release, AstraZeneca, 29 May 2002). A sustained-release formulation is also under development (quetiapine fumarate, SR; qv). Marketing

**It is launched in >20 countries including the UK, the US (1997),** Bulgaria, Thailand (1999), Australia, Germany, Italy, Spain (2000), Belgium, Japan, New Zealand (2001), China (2002), Ireland (2004), Argentina, Brazil, Canada, Denmark, Finland, Hong Kong, Israel, Malaysia, Mexico, the Netherlands, Norway, the Philippines, Portugal, S Korea, Switzerland and Turkey for the 1st-line treatment of schizophrenia, and approved in >75 countries, including the rest of the EU (excluding
Phase III

In a randomized, double-blind, placebo-controlled trial (BOLDER) in 542 patients with bipolar I or II disorder, quetiapine fumarate 300 (recommended dose) and 600mg/day gave a significantly greater improvement in mean Hamilton Rating Scale for anxiety (HAM-A) score cf placebo including in the following criteria after 8wk: anxious mood, depressed mood, insomnia, tension, intellect and behaviour at interview. Quetiapine fumarate 300 and 600mg/day x8wk gave improvements in mean Montgomery-Asberg Depression Rating Scale scores of -16.7 and -16.4, respectively, cf -10.3 for placebo.

Quetiapine fumarate improved anxiety symptoms from day 8 as measured by the HAM-A scale (Press releases, AstraZeneca, 5 May & 22 Jun 2004; 24th CINP (Paris), 2004, Abs P02.097). In a study in 1447 patients aged 18-65yr with an exacerbation of schizophrenia and 85 elderly patients with psychosis, quetiapine fumarate reduced the incidence of tardive dyskinesia cf conventional antipsychotics (Press release, AstraZeneca, 6 Nov 2000). In a double-blind, randomized, US Phase III study (Trial 99) in 190 patients with manic symptoms of bipolar disorder, quetiapine fumarate 500mg/day + a mood stabilizer (lithium or valproate semisodium; qv) x21 days resulted in a change in mean Montgomery-Asberg Depression Rating Scale scores of -16.7 and -16.4, respectively, cf -10.3 for placebo. Quetiapine fumarate improved anxiety symptoms from day 8 as measured by the HAM-A scale (Press releases, AstraZeneca, 5 May & 22 Jun 2004; 24th CINP (Paris), 2004, Abs P02.097). In a study in 1447 patients aged 18-65yr with an exacerbation of schizophrenia and 85 elderly patients with psychosis, quetiapine fumarate reduced the incidence of tardive dyskinesia cf conventional antipsychotics (Press release, AstraZeneca, 6 Nov 2000). In a double-blind, randomized, US Phase III study (Trial 99) in 190 patients with manic symptoms of bipolar disorder, quetiapine fumarate 500mg/day + a mood stabilizer (lithium or valproate semisodium; qv) x21 days resulted in a change from baseline of -13.76, cf -9.93 for placebo + mood stabilizer, as measured by the Young Mania Rating Scale (YMRS) scores at day 21, and scores of -1.38 and -0.78, respectively, were measured on the Clinical Global Impression for bipolar severity of illness (Scrip Daily Online, 13 Sep 2002, S00770876). Three further worldwide Phase III trials for the treatment of acute manic episodes of bipolar disorder are underway. Trial 100 will evaluate quetiapine fumarate as an adjunctive treatment to a mood-stabilizing agent in 220 patients in centres in Africa, W and S Europe and N America; Trial 104 will compare quetiapine fumarate and haloperidol as monotherapy in Asia, E Europe and S America; and Trial 105 will compare quetiapine fumarate and lithium as monotherapy in Asia and E Europe (Press releases, AstraZeneca, 8 Jan 2001 & 6 Jan 2003; Scrip Daily Online, 13 Sep 2002, S00770876). In a pooled analysis of trials 104 and 105 in 604 patients, quetiapine fumarate up to 800mg/day gave a YMRS score of -13.58 from baseline cf -7.76 for placebo after 3wk, and resulted in a response (defined as > or equal to 50% decrease from baseline YMRS) in 48.1% of patients cf 31.3% on placebo, after 3wk. 60.8% of quetiapine fumarate-treated patients completed the trial cf 38.9% of those given placebo (Press release, AstraZeneca, 20 May 2003).

Phase II

In 26 patients with severe, non-psychotic depression who had failed treatment with citalopram (qv), quetiapine fumarate 200mg po improved symptoms of anxiety, depression, guilt, sleep, suicidal ideation and retardation to a greater extent cf haloperidol 3mg po (23rd CINP (Montreal), 2002, Abs P.2.E.037). In a double-blind trial in 95 patients with schizophrenia resistant to fluphenazine, quetiapine fumarate 600mg/day gave a >20% reduction in positive and negative syndrome scale scores in 59% of patients cf 38% of patients treated with haloperidol 20mg/day (Press release, AstraZeneca, 8 May 2001). In a 52wk open-label trial in 184 patients aged >65yr with psychotic disorders due to Alzheimer's disease, Parkinson's disease or schizophrenia, clinically- significant improvement, defined as a >20% decrease from baseline scores on the Brief Psychiatric Rating Scale...
(BPRS), was achieved in 49%. Adverse events were mild-to-moderate somnolence, accidental injury and dizziness (Press releases, AstraZeneca, 1 Nov 1999 & 29 Nov 2000). In a 6wk study in 361 patients with acute exacerbation of schizophrenia, doses in the range of 150-750mg/day were well tolerated and effective against positive and negative symptoms, with a maximal clinical effect at 300mg/day. Across the dose range, there was no difference between quetiapine fumarate and placebo for induction of EPS or elevations of plasma prolactin (20th CINP (Melbourne), 1996, Abs O-22-4 & P-15-6). In 30 adolescent bipolar disorder patients, 87% of patients treated with quetiapine fumarate + valproate semisodium had ≥50% reduction in YMRS scores (from baseline to study conclusion after 6wk) of 53% on valproate semisodium alone (Press release, AstraZeneca, 29 Nov 2001). In an ongoing long-term trial in 28 young patients experiencing their 1st episode of acute schizophrenia, 9 patients who had completed 1yr of treatment with quetiapine fumarate showed significant improvements in cognitive functioning (Press release, AstraZeneca, 27 Apr 2001). In a 12wk open-label study in 17 outpatients with both bipolar disorder and cocaine dependency, 50-100mg improved depression and manic symptoms and reduced cocaine craving (Press release, AstraZeneca, 15 Jun 2001). In an open-label study in 14 neuroleptic responders and 5 neuroleptic-resistant schizophrenia patients, quetiapine fumarate 50-800mg/day significantly improved BPRS positive symptoms, attention, fine motor performance and working memory, but not other measures of cognition at 6wk (Press release, AstraZeneca, 9 May 2001). Astellas discontinued Phase II trials in psychiatric and behaviour disorders associated with dementia (Company pipeline, Astellas, 4 May 2006).

Phase I
In studies, quetiapine fumarate po was well absorbed and extensively metabolized. It had linear pharmacokinetics which did not differ between men and women. The t1/2 was 7hr (Product insert, quetiapine fumarate, 2002).

Preclinical

Additional Clinical Information Post-Marketing
In 129 patients with a history of mental illness and who had been taking quetiapine fumarate for 6mth, 97% preferred quetiapine fumarate to other medications, and 98% expressed desire to continue therapy. 74% Reported no side-effects and 23% reported mild side-effects (Scrip, 1998, 2377, 23). In 34 patients with 1st episode schizophrenia and related mood disorders who were prescribed a mean dose of 517mg quetiapine fumarate q day, attention function scores increased from 1.2 at baseline to 1.8, executive function levels decreased from 4.0 to 1.2 and verbal productivity scores increased from 34.3 to 41.5 (Press release, AstraZeneca, 5 Sep 2002)

In a 12wk international, open-label, multicentre, non-comparative trial (SPECTRUM) in 509 schizophrenia patients who switched to quetiapine fumarate because of inadequate response to or tolerance difficulties with their previous treatments, it delivered significant improvements in all areas of symptom control. The trial, investigating the benefits of switching patients from other antipsychotic agents to quetiapine fumarate, consisted of a 7-day switching phase to quetiapine fumarate 400mg/day, after which flexible dosing was permitted between 300 and 750mg/day (Press release, AstraZeneca, 5 Sep 2002)

Phase III
In a multicentre, placebo-controlled, double-blind trial (Seroquel trial 204,636/0008) in 286 hospitalized patients with acute exacerbation of chronic or subchronic schizophrenia, quetiapine fumarate low (up to 250mg/day) and high (up to 750mg/day) dose was clinically and statistically superior to placebo as assessed by BPRS, CGI and SANS. There were no differences in extrapyramidal side-effects or prolactin levels between either low or high dose seroquel and placebo (Eur Neuropsychopharmacol, 1994, 4, 384).

In a 6wk double-blind trial (Seroquel trial 204,636/0007) in 201 hospitalized patients with acute exacerbations of chronic and subchronic schizophrenia, quetiapine fumarate 75-750mg/day in escalating doses had a comparable efficacy to chlorpromazine. There were no acute dystonic reactions or agranulocytosis (Eur Neuropsychopharmacol, 1994, 4, 385).

In 2387 patients treated with quetiapine fumarate x6wk, incidence of hormonal side-effects, such as sexual dysfunction and menstrual problems, was <1%. In placebo-controlled trials, there were no significant differences in the changes in prolactin levels cf placebo (Press release, Zeneca, Jul 1998)
In a multicentre, double-blind, placebo-controlled, randomized 10wk study in elderly, long-term care patients with dementia, quetiapine fumarate 200mg/day effectively treated dementia-associated agitation (9th Int Conf Alzheimer's Related Dis (Philadelphia), 2004, Abs P2-442).

**Phase II**

In 30 adolescent patients with mania or mixed bipolar I disorder given quetiapine fumarate (mean dose 432mg/kg) subsequent to divalproex sodium 20mg/kg, there was a greater response in treating depressive, manic and psychotic symptoms cf those given placebo (23rd CINP (Montreal), 2002, AbsP2E060, 0).

In the preliminary analysis of a study in 40 patients with rapid cycling bipolar I disorder, quetiapine 170mg/day gave an improvement in HDRS score at 2, 4, 6, and 8wk, and Young Mania Rating Scale (YMRS) score at 2, 4, 6, 12 and 16wk. Clinical Global Impression for Bipolar Disorder score was improved from 2wk. Of 16 patients who withdrew from the trial, 7 did so due to lack of efficacy (23rd CINP (Montreal), 2002, AbsP2E063, 0).

In 41 patients with Parkinson's disease those given quetiapine fumarate 400mg/day for up to 6mth had significant improvements in the BPRS, CGI, NPI-2 and UPDRS psychiatric rating scales cf baseline. These patients also showed significant improvement in sustained attention and memory cf control. There were no significant differences in overall cognitive function or in simple attention between the 2 groups (Scrip Daily Online, 2001, S00702330, 0).

In a double-blind study in 25 patients with schizophrenia in those given quetiapine fumarate 468mg/day, cognitive function was improved at 8wk and for the 6mth period; however, those on haloperidol 15mg/day experienced no significant improvement in cognitive function (Scrip Daily Online, 2001, S00703988, 0).

In a multicentre, double-blind, placebo-controlled trial (Seroquel trial IL/0006) in 109 adult schizophrenic patients, quetiapine fumarate 25mg tid for 1-2 days titrated up to 750mg/day x6wk, significantly improved BPRS, factor IV (activation) and SANS scores cf placebo. There was a marginal improvement in total BPRS, thought disturbance and BPRS positive symptom scores cf placebo. 28% Of quetiapine fumarate-treated patients also showed improvement in the CGI scale cf 25% for placebo.

Quetiapine fumarate did not produce sustained levels of prolactin, with the mean change from baseline at endpoint (7.2microg/l) comparable to placebo (8.2microg/l). Adverse events occurred in >5% and included somnolence, agitation, headache, dry mouth, increased alanine and aspartate aminotransferase, insomnia, constipation, postural hypotension and dizziness (J Clin Pharmacol, 1996, 16, 158).

In 618 patients, 450mg was efficacious against both positive and negative symptoms and was well tolerated, with the incidence of EPS no greater than with placebo. Bid dosing had an improved EPS profile cf tid dosing (20th CINP (Melbourne), 1996, Abs P-22-14) (20th CINP (Melbourne), 1996, AbsP-22-14, 0).

In an open-label clinical trial in 12 patients with schizophrenia or schizoaffective disorder with predominantly positive symptomatology, quetiapine fumarate <750mg/day decreased total scores for BPRS (from 42 to 30), SAPS (64.5 to 36.1) and SANS (55 to 42.5) (Psychopharmacol Berl, 1995, 119, 231).

In a randomized, double-blind trial in 10 schizophrenic patients given quetiapine fumarate, plasma prolactin levels at baseline, day 21 and end of treatment were 25.8, 9 and 17.2ng/ml, respectively, cf 16.0, 7.5 and 7.75ng/ml for placebo. The prolactin levels did not correlate with BPRS or SANS scores. There were no changes in neurological ratings, EPS or reports of hyperprolactinaemia- associated side-effects.

In 151 elderly patients with psychotic disorders given quetiapine fumarate, positive and negative symptoms improved, particularly in patients displaying aggression and hostility (Press release, Zeneca, Mar 1998).

In 12 chronic and subchronic schizophrenics, quetiapine fumarate 25- 250mg/day in escalating doses gave a >35% decrease in BPRS score (17th CINP (Kyoto), 1990, Abs 0-13- 3-8; Scrip 1992, 1778, 15)

In an 8wk, open-label trial in 15 adolescents with schizophrenia or schizoaffective disorder, quetiapine fumarate 25-800mg/day gave a 62% reduction in the BPRS score, a 42% reduction in the CGI scale and a 41% reduction in positive and negative syndrome scale scores (Press release, AstraZeneca, 12 Oct 2001)

Additional References
Eur Neuropsychopharmacol 2004, 14, 299.
21st CINP (Glasgow) 1998.
Arch Gen Psychiatry 1997, 54, 549.
New dibenzothiazepine cpd. with antidopaminergic activity - specifically 11-4-(2-(2-hydroxyethoxyethyl)-1-piperazinyl)-dibenzo(B,F) (1,4)thiazepine

Patent Assignee: ICI AMERICAS INC (ICIL); ZENECA INC (ZENE)
Inventor: MIGLER B M; WARAWA E J

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Priority Applications (no., kind, date): GB 19867684 A 19860327
Alerting Abstract  EP A
11-(4-(2-(2-Hydroxyethoxy) ethyl)-1-piperazinyl) dibenzo(b,f)(1,4)thiazepine of formula (I) and its salts are new: The hemifumarate and hydrochloride salts of (II) are specifically claimed.
USE/ADVANTAGE - (II) has antidopaminergic activity and is useful as (i) an antipsychotic agent and (i) as a CNS depressant for treating hyperactivity. Dose is 1-200 mg/kg/day for small mammals (e.g. dogs) and 1-40 mg/kg/day (sic) for man. (II) has reduced potential to cause side effects (e.g. acute dystonia, acute dyskinesia, pseudo-Parkinsonism as well as tardive dyskinesia cf. known antipsychotics and neurotics.

Equivalent Alerting Abstract US A
11-(4-(2-(2-Hydroxyethoxy) ethyl)-1-piperazinyl) dibenzo(b,f) 1,4-thiazepine of formula (I) and acid addn. salts are new. Pref. salts are hemifurate or hydrochloride salts. Pharmaceutical compns. contg. (I) for treating psychosis or hyperactivity are also claimed. Cpd. (I) can be prepd. e.g. by reacting the 4-unsubstd. 1-piperazinyl dibenzothiazepine with cpd. ZCH2CH2O- CH2CH2OH, where Z is atom or gp. removable as anion, e.g. mesyloxy or halogen.
USE/ADVANTAGE - Cpd. has antidopaminergic activity, with reduced side effects, and is useful as an antipsychotic or for treating hyperactivity.

Title Terms /Index Terms/Additional Words: NEW; DIBENZOTHIAZEPINE; COMPOUND; ANTI; DOPAMINERGIC; ACTIVE; SPECIFIC; HYDROXY; ETHOXY; ETHYL; PIPERAZINYL; DIBENZO; THIAZEPINE; ANTIDEPRESSANT; ANTIPSYCHOTIC; HYDROXY; ETHOXY; ETHYL; PIPERAZINYL