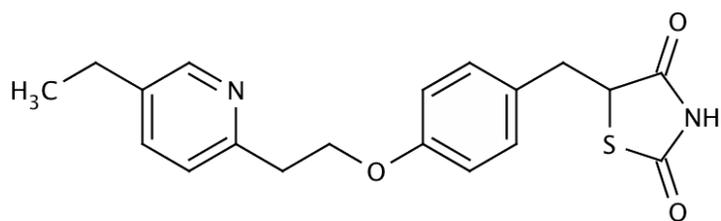


CINAPS Compound Dossier

Pioglitazone



12/22/09

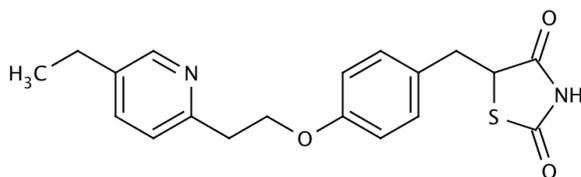
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I. Compound Information

Common name: Pioglitazone

Structure:



Pubchem ID: 4829

Mol. Formula: C₁₉H₂₀N₂O₃S

FW: 356.44

CASRN: 111025-46-8

Polar surface area: 84.8

logP: 2.94

IUPAC name: 5-[[4-[2-(5-Ethyl-2-pyridyl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione

Other names: Actos®, U-72107, AD 4833

Drug class: PPAR-γ agonist

Medicinal chemistry development potential: High

II. Rationale

Ila. Scientific Rationale / Mechanism

Parkinson's disease (PD) is pathologically identified by the progressive loss of dopaminergic neurons in the substantia nigra (SN), resulting in a significant loss of available dopamine in the striatum. Although the cause of death of the dopaminergic neurons has not been established, recent research indicates that chronic local inflammation in the absence of infection may play an important role in initiating the cascade that perpetuates dopaminergic neuronal loss. Many excellent review articles have been written on the role of neuroinflammation in Parkinson's and other neurodegenerative diseases, and how this aspect of the disease can be used to identify neuroprotective therapies.¹⁻⁵

In the brain, inflammation is caused by molecules produced by the glia and neurons.⁶ The microglia, the brain's phagocytic cell, responds to these inflammatory molecules by upregulating CNS inflammation and increasing phagocytosis. Studies of activated microglia in culture with dopaminergic neurons reveal that the microglia can induce the degeneration of the neurons.⁷⁻⁹ Reactive microglia are prominent in the SN and striatum of PD patients, monkeys exposed to MPTP, and in the rodent models of induced PD, including those using 6-OHDA, MPTP, and LPS.³ Humans and monkeys exhibit activated microglia years after exposure to MPTP, suggesting that the inflammatory process remains active long after the initiating event. Induction of activated microglia is accompanied by an increase in nitric oxide synthase (NOS) and cyclooxygenase (COX)-1 and -2 expression through the activation of nuclear factor- κ B (NF- κ B), a key transcription factor in the inflammatory process.¹⁰ In addition, an increase in inflammatory cytokine expression, including interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α), in complement components, and neurotrophic factors was detected in the CNS and striata of PD patients.^{3,6,11} Increased oxidative stress as a result of increased superoxide anion production, which is, in turn, secondary to microglial activation, is considered to be the ultimate cause of dopaminergic neuronal death.

With respect to individual mechanisms of cytotoxicity associated with chronic brain inflammation, the activation of inducible nitric oxide synthase (iNOS) increases the levels of nitric oxide (NO), which has been implicated in neuronal toxicity associated with PD, presumably by means of increased oxidative stress.^{12,13} Compared to control patients, PD patients exhibit an increased density of glial cells expressing iNOS in the SN, suggesting that NO may reach a toxic level in the area of the dopaminergic neurons that are dying.¹⁰ NO can

also cause damage by reacting with superoxide radicals, and altering iron homeostasis, producing free iron that may then be available to generate hydroxyl radicals.¹¹

In addition to iNOS-associated damage, apoptosis is also considered to be an important cytotoxic mechanism in PD. The proinflammatory cytokine TNF α may trigger apoptosis through its receptors located on the dopaminergic neurons in the brain.^{14,15} PD patients have been found to have increased expression of TNF α receptors in the SN, compared to control subjects,¹⁶ thus supporting this hypothesis.¹⁷

PPAR- γ and PD pathophysiology

The peroxisome proliferator-activated receptors (PPAR) are a family of ligand-dependent nuclear hormone receptor transcription factors that are involved in lipid and carbohydrate metabolism, and in immune and inflammatory responses. Each PPAR has a characteristic tissue distribution, and displays specific functions upon binding with endogenous ligands. PPAR- γ is highly expressed in adipose tissue and in cells of the immune system, including lymphocytes and macrophages. In the brain, PPAR- γ is expressed in several cell types including microglia, astrocytes, oligodendrocytes, and neurons.¹⁸ The role of PPAR- γ in lipid homeostasis and insulin sensitivity has been clinically exploited through the use of rosiglitazone and pioglitazone, two thiazolidinedione (TZD) high-affinity synthetic ligands that are prescribed to control blood insulin levels in patients with Type II diabetes. Pharmacological studies indicate that pioglitazone (ACTOS®) improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. However, it is the role of PPAR- γ in the control of inflammation that is most relevant to the treatment of neuroinflammatory diseases, including Parkinson's, Alzheimer's and Huntington's.¹⁸⁻²⁷

PPAR- γ is found to be highly expressed in various brain regions including striatum, substantia nigra, mesencephalon, cortex and hippocampus. Due to its anti-inflammatory action and its ability to inhibit apoptosis, the potent PPAR- γ agonist pioglitazone is currently of considerable interest as a treatment agent for neurodegenerative disorders. Indeed, chronic administration of pioglitazone has been shown to be beneficial in cognitive impairment associated with diabetes and Alzheimer's disease. Pretreatment with pioglitazone has also shown beneficial effects in MPTP-based animal models of Parkinson's disease. However, inhibition of MAO-B and the resulting decreased conversion of MPTP to its toxic metabolite, MPP+, and not its anti-inflammatory activity, has been reported to be the mechanism for these effects.²⁸ Nevertheless, pioglitazone has also shown beneficial effects in an intrastriatal lipopolysaccharide-induced Parkinson's disease model, a therapeutic effect believed to be associated with its reducing

microglial activation, mitochondrial dysfunction and the expression of various inflammatory mediators (NF- κ B and JNK, and suppression of COX-2 activity).²³

IIb. Consistency

In general, pioglitazone has been relatively consistent in its ability to attenuate the progression of inflammation and cell death in several *in vitro* and *in vivo* models of neurodegenerative diseases. However, mechanisms for eliciting beneficial effects clearly varies across these models and this should be taken into consideration in assessing consistency of evidence for pioglitazone's potential therapeutic efficacy. As mentioned above, this is particularly true for the apparent efficacy of pioglitazone in MPTP-treated animal models, where it has been recently shown that inhibition of MAO-B and the resulting decreased conversion of MPTP to MPP⁺ is thought to be responsible for its apparent therapeutic efficacy in that particular model.²⁸

III. Efficacy (Animal Models of Parkinson's Disease)

IIIa. Animal Models: Rodent

Available efficacy data for pioglitazone in Parkinson's animal models include the MPTP mouse model, and the lipopolysaccharide (LPS) model in rats.

MPTP studies in mice. Male C57BL/6 mice (10-12 weeks old) were treated with pioglitazone in the feed (20 mg/kg/day) for 3 days prior to MPTP treatment, and continuing until 2, 5, or 8 days after completion of MPTP treatment (total of 6, 9, or 12 days).²⁹ Pioglitazone prevented dopaminergic cell (TH+) death in the substantia nigra pars compacta (SNpc), and attenuated microglial activation (thought to contribute to neurodegeneration), iNOS-positive glia, and glial fibrillary acidic protein (GFAP)-positive cells. It did not provide protection from dopamine depletion or dopaminergic cell (TH+) death in the striatum. Pioglitazone provided consistent protective effects across days 2, 5, and 8 after MPTP treatment. In another study from the same laboratory, Dehmer, *et al.* used a similar treatment paradigm to establish a correlation between pioglitazone effects.³⁰ C57BL/6 mice were treated with pioglitazone in feed (20 mg/kg/day) for 4 days prior to MPTP treatment until 7 days after completion of MPTP treatment (total of 16 days). Pioglitazone prevented dopaminergic cell (TH+) death in the SNpc, and attenuation of microglial activation (thought to contribute to neurodegeneration), iNOS-positive glia, and GFAP-positive cells. Pioglitazone provided partial protection from dopamine depletion in the SN, suggesting some cell death did occur (no TH+ analysis). In mice dosed with MPTP for 2 days, pioglitazone protected against activation of NFκβ in the SN, which has been linked to cell death.

MPTP studies in rats. Rats were administered pioglitazone (10 and 30 mg/kg, p.o.) starting 5 days prior to MPTP administration and then for next 30 days.³¹ MPTP-lesioned rats improved cognitive performance in passive avoidance task and cued version of the Morris water maze test. Furthermore, pioglitazone treatment also reduced oxidative stress (as evident by reduced malondialdehyde and increased glutathione levels).

LPS studies in rats. Male SD rats (3 months old) were treated with 20 mg/kg/day pioglitazone 4 days prior to and 3 or 7 days after intrastriatal injection with 32 μg LPS from *S. minnesota*, which induces an inflammation-driven dopaminergic neurodegeneration that models PD.²³ Only results from 7 days post LPS treatment were presented. Pioglitazone protected against LPS-induced inflammatory response (COX-2) in the striatum, and attenuated the increase in iNOS and IRβ. It also partially restored decreased mitochondrial respiration in the striatum, and restored mitochondrial respiration in the substantia nigra. Mitochondrial oxidative stress was attenuated in the striatum, but not the substantia nigra. In addition, pioglitazone partially

restored dopamine levels in the striatum, and protected against loss of tyrosine hydroxylase immunoreactive (TH+) dopaminergic neurons in the substantia nigra. No mention was made of animal toxicity or morbidity at these doses. In another study, Hunter, *et al.* looked at the effect of pioglitazone on three mechanistic markers of LPS-induced inflammation in the striatum.³² Male SD rats (3 months old) were treated with 0 or 20 mg/kg/day pioglitazone 4 days prior to and 3 days after intrastriatal injection with 32 µg LPS from *S. minnesota*. The authors looked at the effect of pioglitazone on: (1) induction of PPAR-γ expression, activation of which decreases inflammation, (2) induction of mitochondrial uncoupling protein (UCP2), a response to oxidative stress, and (3) induction of mitoNEET, a mitochondrial membrane protein thought to be involved in the control of mitochondrial metabolism. Pioglitazone prevented the LPS-induced increase in all three of these parameters.

IIIb. Animal Models: Non-human Primates

Partial neuroprotective action of pioglitazone was reported in a monkey model of unilateral Parkinson's disease.³³ Vervet monkeys were given 2.5 mg/kg/day pioglitazone or vehicle in a daily oral dose for three weeks. MPTP (0.15 mg/kg) was then given *i.v.* unilaterally into the internal carotid artery to both groups of monkeys. Oral dosing with pioglitazone or vehicle continued for an additional 4 weeks after MPTP lesioning. Pioglitazone-treated animals exhibited only mild behavioral impairment, compared to the control animals, that exhibited circling toward the side of the lesion, tremors and rigidity in the contralateral side of the body, and lack of use of the contralateral limb. At necropsy, the number of tyrosine hydroxylase immunoreactive dopamine cells (TH-IR) in the substantia nigra pars compacta (SNpc) was only reduced 10-15% on the lesioned side of pioglitazone-treated animals, compared to a 40-52% reduction in cell number in the control animals. This protective effect of pioglitazone was not observed for optical density measurements of TH-IR and dopamine transporter-IR in the striatum (decrease of 70-90%), or for MPTP-induced increases in striatal GFAP-IR on the lesioned side.

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

No clinical studies of the effect of pioglitazone on PD were found. However, several studies of the effects of pioglitazone or rosiglitazone (another thiazolidinedione PPAR- γ agonist) on neurodegenerative diseases other than PD were found. These studies are summarized below in Section V.

IVb. Epidemiological Evidence

Although there is little or no epidemiological data describing the neuroprotective effect of pioglitazone on PD, studies of NSAIDs and PD have been published. Based on the data that indicate that NSAIDs including ibuprofen, indomethacin, naproxen, etc., are PPAR- γ agonists, epidemiological studies of NSAID use and the prevalence of PD were deemed relevant. These studies were reviewed and summarized in Asanuma and Miyazaki.³⁴ In a prospective study of two cohorts (total of 143,000 people), regular non-aspirin NSAID use was associated with a 45% reduction in the prevalence of PD, compared to subjects who did not use NSAIDs. More specifically, another study showed that ibuprofen use was related to a 35% lower risk of developing PD compared to nonusers (total of 146,000 people) . Studies have also shown that non-aspirin NSAID use exerted a protective effect for men, but not for women. Not all studies indicate an effect of NSAIDs, however. More recently published studies show no association between the use of non-aspirin NSAIDs and decreased risk of developing PD. Reviewers have noted that since not all NSAIDs are PPAR- γ agonists, evaluation of the neuroprotective activity of NSAIDs as a group is inappropriate, and is likely masking relevant results. Studies of specific NSAID use and PD should be designed to evaluate individual NSAIDs.

V. Relevance to Other Neurodegenerative Diseases

In a transgenic mouse model of Alzheimer's Disease (AD), pioglitazone treatment of aged APPV717I mice markedly decreased microglial and astroglial activation.³⁵ Importantly, these researchers also observed a significant reduction of the total area and staining intensity of A β 1-42-positive amyloid deposits in the hippocampus and cortex (25 and 33% decrease, respectively), and a 27% reduction in the cerebral levels of soluble A β 1-42 peptide. These findings demonstrate that anti-inflammatory drugs can act rapidly to inhibit inflammatory responses in the brain and negatively modulate amyloidogenesis. Since the β -amyloid peptides that accumulate in Alzheimer's disease plaques also increase the build up of the α -synuclein protein, which is characteristic of the brains of patients with Parkinson's disease, these data also suggest that pioglitazone may be dually effective against both Alzheimer's and Parkinson's disease.

Based on pioglitazone's anti-inflammatory activity, Pershadsingh, *et al.* evaluated its clinical usefulness in the treatment of a patient with MS.³⁶ The 44 year-old woman had secondary progressive MS, and, after 24 years, was paraplegic, wheelchair bound, and exhibited dysphagia and mild cognitive impairment. Although steroid therapy had been beneficial in the past, more aggressive therapies were not well tolerated, and she was no longer receiving any pharmacological treatment for her MS. Treatment with pioglitazone was initiated at 15 mg per day (p.o.), and then increased by 15 mg biweekly to 45 mg per day for the duration of the treatment. Assessments of toxicity and clinical effects included blood pressure, metabolic profiles, and edema, as well as MRI, motor function, muscle strength, and cognition. Improvement in attention span, cognition, and appetite were observed within 4 weeks. After 8 months of treatment, the patient exhibited increased extremity strength and improved coordination, and unilateral fine motor coordination, increased short-term memory, and cognition. Overall brain atrophy was arrested, and the patient became clinically stable.

Watson, *et al.* conducted a 6 month, double-blind, placebo-controlled pilot study of rosiglitazone (another thiazolidinedione) in patients with mild AD or amnesic mild cognitive impairment, in which rosiglitazone (4 mg; N = 20) or placebo (N = 10) was administered daily.³⁷ Subjects receiving rosiglitazone exhibited better delayed recall and selective attention, compared to the placebo group. In addition, those receiving rosiglitazone had unchanged plasma levels of β -amyloid (A β), compared to declined levels for subjects receiving placebo, consistent with recent reports that plasma A β 42 decreases with progression of AD.

In an abstract presented at the 10th International Conference on Alzheimer's Disease and Related Disorders, Geldmacher, *et al.* reported the results of a randomized, double-blind,

placebo-controlled, pilot study designed to assess the safety of pioglitazone in nondiabetic patients with AD.³⁸ A total of 29 subjects, mean age of 70.9, with diagnosed probable AD, based on the criteria established by the NINDS/Alzheimer's Association, were randomly assigned to treatment groups receiving placebo or 45 mg pioglitazone daily for 18 months. All study participants also received 200 units of Vitamin E and cholinesterase inhibitors daily. Twenty-five of the 29 participants finished the study. There were no differences between the placebo and pioglitazone groups for hypoglycemia or measures of behavior, function, or cognition. The lack of significant positive effect may have been due to the small sample size. Edema was the primary clinically significant treatment-related adverse effect, observed in 28.6% of the pioglitazone group vs 0% in the placebo group.

Also presented at the 10th International Conference on Alzheimer's Disease and Related Disorders were the results of a 24-week pilot study on the effects of rosiglitazone on the performance of 56 patients with mild to moderate AD in neuropsychological tests.³⁹ These patients were a subset of a larger study (also see Risner, *et al.*).⁴⁰ Baseline responses to standard clinical measures (e.g. ADAS-cog battery) and experimental measures of simple (yes/no) and choice reaction time (left or right visual field) to color changes in a computer-generated display were similar across the treatment groups. Study participants received a daily dose of 0, 2, 4, or 8 mg rosiglitazone. No difference was detected between the placebo and rosiglitazone-treated groups in the results of the cognitive battery. Similarly, simple response time to color change was not affected by treatment. However, the placebo group exhibited an increase in the amount of time (i.e., slower to respond) required to respond to the left/right visual field choice tasks over the course of the study, compared to all three of the treated groups. Statistically significant differences were observed between the placebo and the 2 and 4 mg rosiglitazone groups. The increase in response time to left field changes were more marked, supporting data indicating that preference to the right visual field occurs as contralateral blood flow and attention decreases in AD patients. In this pilot study, rosiglitazone appeared to prevent the progression of AD symptoms.

However, data subsequently reported from the full study suggested there was no benefit of rosiglitazone treatment in AD.^{40,41} Five hundred and eleven subjects with mild-to-moderate AD were randomized to groups receiving placebo or 2, 4 or 8 mg rosiglitazone for 24 weeks. At week 24, the subjects were evaluated for mean change from baseline in the ADAS-Cog battery and Clinician's Interview-Based Impression of Change Plus Caregiver Input global scores. No statistically significant differences on primary end points were detected between placebo and any RSG dose. However, in a subpopulation of the study (n=323) selected for the apolipoprotein E (APOE ε4) allele, there was a significant improvement in ADAS-Cog results in patients who

were APOE ϵ 4 negative and received 8 mg rosiglitazone. No improvement and some decline in mental acuity was observed in APOE ϵ 4 positive subjects.

VI. Pharmacokinetics

VIa. General ADME

Pioglitazone (as ACTOS®) is typically administered once daily without regard to meals. Following oral administration, the active pharmaceutical ingredient, pioglitazone, is well-absorbed, with a mean absolute bioavailability of 83%, and serum levels reaching maximum concentrations in around 1.5-2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. It is metabolized by the hepatic cytochrome P450 enzyme system. However, unlike troglitazone, another thiazolidinedione PPAR- γ agonist with putative antidiabetic and anti-inflammatory properties, studies have provided little evidence to suggest that pioglitazone administration leads to inhibition or induction of any of the P450 isoenzymes involved in drug metabolism. Therefore pioglitazone may have lower potential for drug interaction. The half-life is about 9 hours but two active metabolites mainly contribute to the extended glucose-lowering effects. After oral dosing, serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with Type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC). Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day. The pharmacokinetics are not significantly altered in Type 2 diabetes, renal or hepatic insufficiency or in the elderly.⁴²

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean \pm SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. Thus, pioglitazone is extensively metabolized by hydroxylation and oxidation; the

metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. As described earlier, at steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Vib. CNS Penetration

When administered systemically to mammals, 18% of pioglitazone enters the CNS within 6 h of administration.⁴³ Thus, it appears that within the thiazolidinedione class of PPAR agonists, pioglitazone is one of the only compounds that penetrate the blood-brain barrier to a significant extent. However, this can still be considered a relatively low degree of brain penetration, which has been hypothesized to be responsible for decreased efficacy in the treatment of CNS pathologies such as Alzheimer's disease and other neurodegenerative disorders.⁴⁴

Vic. Calculated log([brain]/[blood])

-0.67 (Clark model⁴⁵)

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

The primary adverse effect seen with thiazolidinediones such as pioglitazone is fluid retention. This can lead to or exacerbate congestive heart failure in some patients. Symptoms of heart failure, including excessive, rapid weight gain, dyspnea, and edema may develop over time, and discontinuation or dose reduction of pioglitazone must be considered.⁴⁶

Due to the ability of thiazolidinediones to produce fluid retention and edema, pioglitazone is not recommended for treatment in patients with symptomatic heart failure or liver disease. Initiation of pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. In addition, therapy with thiazolidinediones should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy. Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women.

Thiazolidinediones such as pioglitazone are also associated with liver disease. Liver enzyme monitoring is recommended in all patients prior to initiation of therapy and periodically thereafter. During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with pioglitazone had ALT values ≥ 3 times the upper limit of normal during treatment. Fewer than 0.9% of patients treated with pioglitazone were withdrawn from clinical trials in the U.S. due to abnormal liver function tests. However, during clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). These elevations resolved without any apparent clinical sequelae.

Pioglitazone may cause dose-related decreases in hemoglobin and hematocrit. These changes appear to be related to increased plasma volume associated with thiazolidinedione therapy and have rarely been associated with any significant hematologic clinical effects.

VIIb. Drug Interaction Potential

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate. In addition, an enzyme inhibitor of CYP2C8 may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 may significantly decrease the AUC of pioglitazone. For example, rifampicin induces P450s, which results in a significant decrease of area under the plasma concentration-time curve [AUC] (54-65% for rosiglitazone,

p<0.001; 54% for pioglitazone, p<0.001), whereas gemfibrozil inhibits P450s, which results in a significant increase of AUC (130% for rosiglitazone, p<0.001; 220-240% for pioglitazone, p<0.001).

The following drug interactions in healthy volunteers with co-administration of ACTOS® 45 mg once daily have also been reported:

Administration of ACTOS® for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Co-administration of ACTOS® for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Co-administration of ACTOS® for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Co-administration of ACTOS® (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinylestradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinylestradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinylestradiol pharmacokinetics, the clinical significance of this finding is unknown.

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