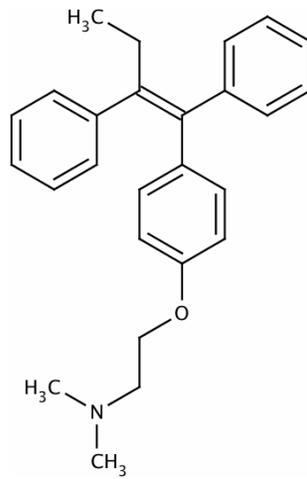


CINAPS COMPOUND DOSSIER

Tamoxifen



4/26/2010

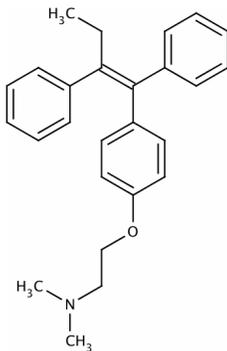
Table of Contents

I. Compound Information.....	3
II. Rationale.....	4
IIa. Scientific Rationale / Mechanism.....	4
IIb. Consistency.....	6
III. Efficacy (Animal Models of Parkinson’s Disease).....	7
IIIa. Animal Models: Rodent.....	7
IIIb. Animal Models: Non-human Primates.....	7
IV. Efficacy (Clinical and Epidemiological Evidence).....	8
IVa. Clinical Studies.....	8
IVb. Epidemiological Evidence.....	8
V. Relevance to Other Neurodegenerative Diseases.....	9
VI. Pharmacokinetics.....	10
VIa. General ADME.....	10
VIb. CNS Penetration.....	11
VIc. Calculated $\log([\text{brain}]/[\text{blood}])$	11
VII. Safety, Tolerability, and Drug Interaction Potential.....	12
VIIa. Safety and Tolerability.....	12
VIIb. Drug Interaction Potential.....	13
VIII. Bibliography.....	15

I. Compound Information

Common name: Tamoxifen

Structure:



Pubchem ID: 5376 **Mol. Formula:** C₂₆H₂₉NO **FW:** 371.515

CASRN: 10540-29-1 **Polar surface area:** 12.47 **logP:** 7.88

IUPAC name: 2-{4-[(1Z)-1,2-Diphenylbut-1-en-1-yl]phenoxy}-N,N-dimethylethanamine

Other names: Nolvadex®, Istubal®, Valodex®

Drug class: Estrogen receptor antagonist

Medicinal chemistry development potential: High

II. Rationale

Ila. Scientific Rationale / Mechanism

The use of tamoxifen (TAM) in the treatment of PD was initially predicated on the observations that (1) incidence of the disease is low in women compared to men, (2) TAM improves motor problems in post-menopausal women with PD, and (3) estrogen replacement therapy helps women in the early stages of PD who are not taking L-DOPA, all suggesting an estrogenic basis for protection from the disease.¹ TAM possesses anti-estrogenic, estrogenic, or mixed effects depending on the species, tissue and gene target.¹⁻² TAM has a better safety profile than estrogen³⁻⁶ prompting the investigation of its use in the treatment of PD. While the efficacy of TAM in treating breast cancer is clearly tied to its action as an antagonist of the estrogen receptor, the literature reviewed suggests that mechanisms other than those mediated by genomic ER responses are important in the efficacy of TAM in Parkinson disease and include (1) inhibition of protein kinase C (PKC) and modulation of other signal-transduction pathways such as (2) mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), (3) phosphatidyl inositol-3-kinase (PI3K) and protein kinase B (Akt), (4) anti-oxidant activity of TAM mediated by signal transduction, and (5) modulation of neurotransmitter levels and transport.

Estrogen Receptor (ER) Antagonism

The literature, particularly earlier citations, presented an ambiguity as to the beneficial effects of TAM in its interaction with the ER. Much of the literature demonstrating a neuroprotective effect of estradiol attributed that effect to activation of the ER, and that its beneficial effect was abolished by coadministration with the ER antagonist TAM. Accordingly, in SK-N-SH neuroblastoma cell cultures, TAM abolished the protective effect of estradiol in MPTP treated cells.⁷ However, administered alone, TAM was neuroprotective against the effects of methamphetamine and MPTP in mice, but here again abolished the protective effects of estradiol when they were given together.⁸⁻¹¹

More recent citations provided an elaboration on this seeming ambiguity.^{8, 12-13} Manganese toxicity (manganism) resembles PD in that it presents with generalized bradykinesia and widespread rigidity, and both are characterized by altered glutamate homeostasis. Both estrogen and TAM protect against manganism. Lee, *et al.*¹²⁻¹³ attribute distinct mechanisms for their respective actions, with estrogen acting by mechanisms that include genomic responses, while concluding that those involving TAM are “not mediated by classical ER-dependent mechanisms”, but instead by action at membrane-associated ER receptors. In these experiments the pure ER antagonist, ICI 182,789, blocked protection. However, a potential ER agonist role of TAM in protection from ischemia was excluded by experiments showing that ICI 182,789 had no effect on neuroprotection conferred by TAM.¹⁴

PKC Inhibition and Signal Transduction through MAPK/ERK, PI3K/Akt Kinases

Tamoxifen is a potent PKC inhibitor which is approved for human use.¹⁵ The role of phosphoinositide and PKC signal transduction pathways in brain functioning has been comprehensively reviewed by.¹⁶ PKC is heterogeneous in brain, and is expressed at high levels in presynaptic terminals. These calcium-activated, phospholipid-dependent protein kinases play a major role in regulating both pre- and postsynaptic aspects of neurotransmission.¹⁷⁻¹⁹

Activation of neurotransmitter receptors can induce rapid, transient changes in the membrane potential of effector neurons that last on the order of milliseconds. This brief activation of neurotransmitter receptors can also induce changes in neuronal function that last minutes, hours, or even days and months. Such long-lasting changes in neuronal function play a critical role in regulating behavior and can include changes in electrochemical potential or in important cellular processes, such as neurotransmitter synthesis, neurotransmitter release, and gene expression.²⁰⁻²¹ Generally, post-translational effects of specific protein kinases bring about changes in neuronal function that persist after the activation of neurotransmitter pathways. Although inositol phospholipids are relatively minor components of cell membranes, they play a major role in receptor-mediated signal-transduction pathways and are involved in a diverse range of responses, such as cell division, secretion, and neuronal excitability and responsiveness.¹⁶ PKC is regulated through the phosphoinositide (PI) cycle, where hydrolysis of inositol phospholipids forms diacylglycerol, which activates PKC. PKC in turn regulates MAPK, and the activity of other key phosphoprotein substrates, including myristoylated alanine rich C kinase substrate (MARCKS), which plays a role in long-term events surrounding cellular plasticity, learning and memory. The MAPK/ERK and PI3K/Akt signaling pathways attenuate damage caused by reactive oxygen species and have a general neuroprotective role.^{8, 12-13} Activation of these pathways by TAM has been shown to protect against manganese toxicity¹²⁻¹³ and confer an antiapoptotic effect *in vitro* in cortical astrocytes.²² MAPK/ERK and PI3K/Akt regulate transforming growth factor TGF- β 1. It is important in rescuing neurons in excitatory, β -amyloid, apoptotic and ischemic models, and is upregulated by TAM.²² Lee, *et al.*¹² conclude that TGF- β 1, which is upregulated by ischemia-induced brain damage, plays a critical role by regulation of the glutamate/aspartate transporter (GLAST) and the glutamate transporter GLT-1. Since elevated extracellular levels of glutamate are associated with excitotoxicity, removal of glutamate by GLAST and GLT-1 are critical for homeostasis.

PKC is involved in phosphorylation state of striatal AMPA receptors and may accelerate the onset of L-DOPA-associated motor changes.²³ PKC isoforms ϵ and λ are the forms associated with motor complications induced by L-DOPA. In 6-hydroxydopamine lesioned rats and MPTP treated monkeys, TAM (1-5 mg/kg) significantly attenuated L-DOPA-induced motor complications and inhibited the expression of the associated PKC isoforms ϵ and λ , while leaving the other isoforms unaffected.²⁴

Other Effects on Neurotransmitters

The protective effect of TAM against methamphetamine-induced nigrostriatal dopaminergic toxicity was studied in mice.⁸ TAM prevented methamphetamine-induced decreases in striatal dopamine and binding to the monoamine vesicular transporter (VMAT2). VMAT2 is reduced in PD patients.²⁵ TAM stimulates endogenous release of dopamine, but does not affect reuptake.^{9, 24}

Antioxidant/ischemia/ROS

TAM protects against damage caused by radicals formed during ischemia in an occlusion/reperfusion model.¹⁴ TAM reduced infarct volume >80%. Protective mechanisms demonstrated by those authors include inhibition of the release of excitatory amino acids that occurs with swelling, inhibition of neuronal nitric oxide synthase activity, and scavenging of reactive oxygen species (ROS) and other reactive species. Tamoxifen was effective even when administered 3 h after the initiation of ischemia, and reduced isoprostanes (markers of free radical damage) to control levels. The major tamoxifen metabolite, 4-OH tamoxifen, was shown to markedly reduce induced lipid peroxidation in brain mitochondria *in vitro*.²⁶ TAM attenuated manganese-induced production of ROS in cultures of neurons and astrocytes^{12, 27} demonstrated that TAM protects against MPTP-induced hydroxyl radical formation in rat striatum.

Efficacy in Mania

The efficacy of TAM in the treatment of mania, investigated specifically as an inhibitor of PKC, suggests that beneficial biochemical sequelae to PKC inhibition may also be of value in the treatment of PD.²⁸⁻³⁰

IIb. Consistency

n/a

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

IIIa. Animal Models: Rodent

Summaries of the pharmacokinetics, general ADME and safety and tolerability of TAM in rodent models are provided in those respective sections. As most research with TAM involved breast cancer endpoints, there were limited citations describing experiments using animal models to determine the utility of using TAM to treat the symptomology associated with PD.

In mice, TAM (subcutaneous doses of ca. 0.6-25 mg/kg) protected against methamphetamine- and MPTP-induced dopaminergic toxicity, diminishing the decreases in striatal dopamine and binding to the monoamine vesicular transporter (VMAT2) caused by those challenges. VMAT2 is a relevant marker in that it is reduced in PD patients.²⁵ Dluzen, *et al.* also reported a protective effect of TAM (5 mg, 21 day, s.c. implant) against methamphetamine-induced depletion of dopamine in male and female mice.³¹

In rats made 'Parkinsonian' by lesioning with 6-hydroxydopamine, TAM (5 mg/kg, oral) prevented as well as ameliorated the characteristic shortening in duration of motor response to L-DOPA challenge. This beneficial effect was attributed to inhibition of the expression of PKC isoforms ϵ and λ that are associated with motor response problems caused by chronic L-DOPA treatment; other PKC isoforms were unaffected.²⁴ Obata, *et al.* demonstrated that TAM (dosed *via* microdialysis) protects against MPTP-induced hydroxyl radical formation in rat striatum.²⁷

In an occlusion model in rats, Zhang, *et al.* demonstrated that TAM (5 and 10 mg/kg, intracisternal) reduced markers of oxidative stress and improved neurobehavioral deficit scores measured 24 h after initiation of ischemia.¹⁴ TAM was as effective when administered at occlusion or at 3 h following the procedure.

IIIb. Animal Models: Non-human Primates

As was the case with rodent models, most research with TAM reported in the literature involved breast cancer endpoints. There were limited citations describing experiments using non-human primates to determine the utility of using TAM to treat the symptomology associated with PD.

Smith, *et al.* found that TAM (1 mg/kg oral) significantly attenuated L-DOPA-induced dyskinesias in MPTP-treated monkeys.²⁴

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

The pharmacokinetics of TAM in humans is detailed in Section VI, and the safety, tolerability, and quality of life assessment of a large cohort of breast cancer patients is summarized in Section VIIa.

Clinical studies relevant to the efficacy of specifically treating PD with TAM were not found, but there were three reports of its use in treatment of mania/bipolar disease. Yildiz, *et al.* (2008) conducted a three-week, randomized, double-blind, placebo-controlled, parallel-arms trial of TAM in sixty patients (equal number of men and women).²⁸ TAM (40-80 mg/day, p.o.) demonstrated anti-manic properties and was well-tolerated. In a placebo-controlled study, Zarate et al (2007) found TAM (20-140 mg/day) produced significant improvement in mania as early as five days into the trial, with the effect lasting throughout the 3-week course of treatment.³⁰ In an early study, Kendler, *et al.* (2000) investigated the use of TAM (20-80 mg/kg) for treatment of mania in a group of five men and two women. Treatment with TAM resulted in a significant decrease in manic symptoms as rated by the Young Mania Rating Scale.²⁹

IVb. Epidemiological Evidence

Epidemiological investigation points to an increased risk of PD in conditions causing an early reduction in endogenous estrogens (early menopause, reduced fertile life length) and long cumulative length of pregnancies has been associated with an increased PD risk in women.³² In this context, the known selective estrogen receptor modulator (SERM) activities of TAM support its consideration for the treatment of PD.¹

V. Relevance to Other Neurodegenerative Diseases

Parkinson disease is often related mechanistically to brain injury, such as that caused by occlusion or ischemia, and to the striatal dopaminergic toxicity induced by MPTP and 6-hydroxydopamine. The efficacy of TAM in ameliorating those symptoms is described in the Scientific Rationale/Mechanism section.

The balance of the literature suggests that modulation of PKC, as well as non-genomic estrogen receptor interactions, confer the therapeutic activity of TAM. TAM and other PKC inhibitors show promise in the treatment of mania, a symptom of PD.²⁸⁻²⁹

Manganese toxicity (manganism) resembles PD in that it presents with generalized bradykinesia and widespread rigidity, and both are characterized by altered glutamate homeostasis. As described in the Scientific Rationale/Mechanism section, TAM protects against manganism through expression of transporters and proteins key to proper neurological functioning.¹²⁻¹³

VI. Pharmacokinetics

Via. General ADME

In human subjects, TAM is predominantly metabolized to N-desmethyl TAM in the liver, which has anti-estrogenic activity similar to TAM, and lesser amounts of the potent metabolite, 4-hydroxy TAM (4-OH TAM); both of these metabolites can be converted to 4-hydroxy-N-desmethyl TAM. TAM N-oxide and 4'-hydroxy TAM are also found, but these metabolites are of low activity.³³ TAM is marketed as the *trans*-isomer, but metabolic *cis/trans* isomerization of 4-OH TAM yields the *cis*-isomer, a weak estrogenic agonist.³⁴ There is potential for further oxidation of 4-OH TAM to a catechol, and potentially further transformed to a reactive quinone.³⁴⁻³⁵

Cytochrome P450 (CYP) is the major enzyme catalyzing the clearance of TAM, and its conversion to its most active antiestrogenic metabolite, *trans*-4-hydroxy TAM, as well as N-desmethyl TAM, 4'-hydroxy TAM, the 4-hydroxy *cis*-isomerization product.³⁴ N-Desmethyl TAM has ER activity roughly that of TAM, and 4-hydroxy-N-desmethyl TAM retains high affinity for the receptor. Increased *cis/trans* ratios are associated with clinical resistance to TAM therapy.³⁴ In addition to cytochrome P450, flavin-containing monooxygenase (FMO) also catalyzes the oxidation of TAM, yielding TAM N-oxide.

Crewe, *et al.* (2002) investigated the metabolism of TAM by human recombinant human enzymes CYP1A1, 1B1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5, and 3A7 *in vitro* at concentrations of 18 and 250 μM .³⁴ Steady state concentrations of TAM in human clinical trials are approximately 0.5 μM , indicating that *in vitro* investigations at the lower *in vitro* concentration is more physiologically relevant. CYP2D6 proved to be the major catalyst of 4-hydroxylation of TAM at the lower concentration. N-demethylation at this concentration was catalyzed by CYP2D6, as well as by CYP1A1, 1A2, and 3A4. Although CYP2D6 is responsible for TAM activation *via* 4-hydroxylation, paradoxically, high genotypic expression of this enzyme correlates with high drop-out rates in clinical trials.³⁶ CYP1B1 was the major catalyst of *cis/trans* isomerization, with some contribution of CYP2B6 and CYP2C19.

Genotypes expressing high UGT2B15 and SULT1A1 (glucuronyl transferase and sulfotransferase enzyme forms, respectively) are associated with increased risk of cancer recurrence and poorer survival rates.³⁷ These phase II enzymes conjugate and terminate the activity of the active metabolites. Consistent with this, in patients TAM is mostly eliminated as conjugates of deaminated metabolites in the stool after enterohepatic circulation.²

TAM is a mechanism-based inhibitor of CYP2B6 with a K_i of 0.9 μM , which is within the clinically relevant range.³⁸ TAM did not inhibit CYP1B1, or 3A4, but some time-dependent (mechanism-based) inhibition of CYP2D6 and CYP2C19 was observed (about 25% loss). Those authors conclude that a drug interaction could occur if TAM is co-administered with a drug that is

metabolized by CYP2B6 only, or by CYP2B6 with contributions of CYP2D6 and CYP2C19.

In rat, 4-hydroxyandrostenedione, an inhibitor of both CYP3A and aromatase, inhibits TAM metabolism.³⁵ As this inhibitor may potentially be used in combination therapy with TAM, modulation of the formation of activated/deactivated metabolites and diminution of reactive metabolites may result from this regimen.

In clinical studies, it was demonstrated that TAM is readily absorbed following oral administration, with a T_{max} of 3-7 h.^{33, 39}

Continuous therapy with TAM (10 mg b.i.d., p.o.) produces steady state levels of 100-200 ng/ml serum within 4-6 weeks. Levels of one of the two major active metabolites, N-desmethyl TAM, were often up to twice the levels achieved with TAM, but the other, 4-hydroxy TAM, were less than 10 ng/ml. The half-life of TAM is about 7 days, and that of the two active metabolites was about 14 days.⁴⁰ In another report two elimination phases were described, an initial half-life of 7-14 h and a terminal half-life of 4-11 days. Consequently, steady state was reached in 3-4 weeks in that study.²

In rats administered a 0.36 mg/kg iv dose of TAM, a concentration of 35 ng/mL TAM was detected in blood, but much higher levels (200-400 ng/g tissue) were found in brain.⁴¹ The pharmacokinetic area under the curve ratio for brain vs. blood was 18 for the 0-4 hour interval.

Vib. CNS Penetration

There is direct and indirect evidence that TAM penetrates well into the CNS in human subjects and rats. Biegon, *et al.* (1996) administered TAM (0.36 mg/kg *iv*) to rats, and measured its concentration in blood and brain.⁴¹ TAM rapidly penetrated into brain, and the pharmacokinetic area under the curve ratio for brain vs. blood was 18 for the 0-4 hour interval, a very high value for a drug. The protective effect of TAM against toxic insults to the brain caused by methamphetamine, manganese, MPTP and stroke, occlusion, or reperfusion in rodent models (as described in the Scientific Rationale/Mechanism section, *vide supra*) also indicates that therapeutic levels of TAM reach the brain.

Penetration of TAM into the brains of patients with malignant gliomas was demonstrated in radiographic studies.⁴² The efficacy of TAM in the treatment of mania also suggests that therapeutic levels reach the brain.²⁸⁻³⁰

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

1.17 (Clark Model⁴³)

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

General

The safety of TAM has been assessed almost entirely in women undergoing treatment for breast cancer; however, the incidence of PD is higher in men. TAM is described as well-tolerated in all studies in which an assessment was made.^{28, 44-46} In three studies using TAM for the treatment of mania, at least half of the patients were male. Using a dosing regimen starting at 20 mg b.i.d, p.o. and building to 80 mg/day, Yildiz, *et al.* (2008) noted that TAM was remarkably well-tolerated; patients experienced no change in blood pressure, pulse, or typical clinical chemistries such as serum transaminases.²⁸ Similarly, TAM has been found to be well-tolerated in patients (5 male, 3 female) being treated for mania.²⁹⁻³⁰ In a broad (11,064 patients) quality of life study of TAM in breast cancer patients, TAM was associated with increases in vasomotor and gynecological symptoms, as well as problems with sexual function.⁴⁵ However, patients reported that their overall physical and emotional well-being was not affected.

Common adverse reactions to tamoxifen include vasomotor symptoms (hot flushes), atrophy of the vaginal lining, hair loss, nausea and vomiting. These may occur in as many as 25% of patients and are rarely sufficiently severe to require discontinuation of therapy.^{33, 45}

Gynecological Effects

Gynecological side-effects may limit the use of TAM in women. These effects include endometrial hypertrophy^{33, 47}, menstrual irregularities, vaginal bleeding and discharge, pruritus vulva, and dermatitis occur frequently, depending on the menopausal state of the women.^{33, 45} TAM increases the incidence of endometrial cancer by 2-3 fold, particularly in older post-menopausal women who took 20 mg TAM/day for 2 years or more.^{2, 48}

Ocular effects

TAM induces retinopathy following chronic high dose therapy (180-240 mg/day) for 2 years.⁴⁹ There was widespread axonal degeneration in the macular and perimacular area. Clinical symptoms include a permanent decrease in visual acuity and abnormal visual fields, and the axonal degeneration was irreversible.^{46, 50-51} At low chronic doses (20 mg/day) there were small but statistically significant increases in the incidence of keratopathy (degeneration of cornea) and a lower incidence of retinopathy than at the high dose; following cessation of therapy, most of the symptoms proved reversible, except the corneal opacity and retinopathy.⁴⁶ The permanent changes include decrease in visual acuity and abnormal visual fields.

Coagulation, coronary effects, and serum lipids

There were reports of adverse effects in the coagulation system (thromboembolism) in women taking TAM,³³ including deep-vein thrombosis and pulmonary embolism (2-3 fold increases).⁵²⁻⁵³

These TAM-induced increases in thrombotic events are thought to occur due to an increased production of clotting factors in the liver.⁵⁴ However, there were also beneficial effects, including lower rates of myocardial infarction and of hospitalization for heart disease. TAM lowers total serum cholesterol, LDL cholesterol, and lipoproteins, and raises apolipoprotein A-I levels, potentially decreasing the risk of myocardial infarction.^{33, 55}

Drug Interaction

As described in the Section VIIIb, Drug Interaction Potential, TAM has low potential for causing drug interactions at clinically-relevant doses. At higher doses, TAM may significantly inhibit the clearance of drugs predominantly metabolized by CYP2B6.

Beneficial Effects

In addition to the beneficial effects of serum lipids and on lower rates of myocardial infarction noted above, TAM increases bone density, and may slow osteoporosis.³³

Cancer

Like estrogen, TAM is a hepatic carcinogen in animals, but increases in primary hepatocellular carcinoma have not been reported in patients on the drug.³³ As noted above in the Gynecological Effects section above, TAM increases the incidence of endometrial cancer.

VIIIb. Drug Interaction Potential

No direct drug interaction studies were conducted in human subjects, but literature citations indicating that TAM inhibits key human metabolic enzymes and induces enzymes in rats for which there is significant homology. There is one citation of an interaction between TAM and 4-hydroxyandrostenedione, with which it could plausibly be co-administered in a regimen of treatment.

Cytochrome P450 (CYP) is the major enzyme catalyzing the clearance of TAM, as well as its conversion to its most active antiestrogenic metabolite, trans-4-hydroxy TAM.^{34, 56} N-desmethyl TAM also has ER activity roughly that of TAM. Crewe, *et al.* (2002) investigated the metabolism of TAM by human recombinant human enzymes CYP1A1, 1B1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5, and 3A7 *in vitro* at concentrations of 18 and 250 μM .³⁴ Steady state plasma concentrations of TAM in human clinical trials are approximately 0.5 μM , indicating that *in vitro* investigations at the lower *in vitro* concentrations are more physiologically relevant.³⁹ CYP2D6 proved to be the major catalyst of 4-hydroxylation of TAM at the lower concentration. N-demethylation at this concentration was catalyzed by CYP2D6, as well as by 1A1, 1A2, and 3A4.

TAM is a mechanism-based inhibitor of CYP2B6 with a K_i of 0.9 μM , which is within the clinically relevant range.³⁸ In addition to inhibition of CYP2B6, there was about a 25% loss of CYP2D6 and 2C9 activities at a TAM concentration of 6 μM , but CYP1B1 and 3A4 were not affected. This suggests possible drug interactions when coadministered with other drugs

metabolized by 2B6 only, or by CYP2B6 with contributions of CYP2D6 and CYP2C19.

In rat, TAM induces CYP2B2, 2B1 and 3A at therapeutically relevant doses, indicative of transcription responses regulated by CAR and PXR, respectively.⁵⁷ While these receptors differ somewhat between rat and human, this indicates possible induction of a wide variety of phase I and phase II enzymes regulated by them, with resulting effects on the clearance of other drugs taken by the patient.

In rat, 4-hydroxyandrostenedione, an inhibitor of both CYP3A and aromatase, inhibits TAM metabolism.³⁵ As this inhibitor may potentially be used in combination therapy with TAM, modulation of the formation of activated/deactivated metabolites and diminution of the formation of reactive metabolites may result from this regimen.

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