

**RE: PHARMACOKINETIC PROFILE OF WELLBUTRIN XL®**

**SUMMARY**

- Wellbutrin XL® (bupropion HCl extended-release tablets) is indicated for the treatment of major depressive disorder in adults aged 18 years and older.
- *Wellbutrin XL* demonstrated bioequivalence to Wellbutrin® (bupropion HCl) Tablets in a randomized crossover pharmacokinetic trial of 30 healthy subjects. In a study of similar design, *Wellbutrin XL* demonstrated bioequivalence to Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets in 49 healthy subjects.
- Peak steady-state plasma concentrations on average with *Wellbutrin XL* 300 mg once daily are approximately 17% lower than those achieved with *Wellbutrin* 100 mg three times daily 7% higher than those achieved with *Wellbutrin SR* 150 mg twice daily.
- Bupropion is extensively metabolized with less than 0.5% of a dose excreted unchanged. Bupropion is metabolized primarily via the cytochrome P450 (CYP) 2B6 isoenzyme. The isoenzymes CYP1A2, 2A6, 2C9, 2E1 and 3A4 are also capable of metabolizing bupropion, but at a rate much lower than that for CYP2B6. Bupropion, while not metabolized by CYP2D6, inhibits the activity of this isoenzyme and may inhibit the metabolism of coadministered drugs metabolized by CYP2D6.

**Some information contained in this response may be outside the approved Prescribing Information for *Wellbutrin XL*. This response is not intended to offer recommendations for administering *Wellbutrin XL* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Wellbutrin XL*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Wellbutrin XL*.**

**CLINICAL INFORMATION**

**Bioequivalency of bupropion formulations**

*Wellbutrin XL* is an extended-release formulation of bupropion hydrochloride intended for once-daily administration for the treatment of major depressive disorder in adults aged 18 and older. The US Food and Drug Administration (FDA) has defined specific criteria to establish the bioequivalence of products (1). The 90% confidence interval of the ratio of means for the following primary parameters must be within the 0.8-1.25 range: steady-state maximum plasma concentration ( $C_{max}$ ), area under the curve (AUC) and minimum plasma concentration ( $C_{min}$ ) for bupropion and its metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion) and the pharmacological activity-weighted composite (PAWC) of bupropion and its metabolites. *Wellbutrin XL* demonstrated bioequivalence to the immediate and sustained-release formulations of bupropion in 2 separate pharmacokinetic studies in healthy subjects (2, 3).

The first study was a randomized, open-label, multiple-dose, 2-way crossover study in 30 healthy subjects which compared 14-day dosing with *Wellbutrin XL* 300 mg once in the morning (QAM) with 100 mg of *Wellbutrin* dosed 3 times daily (TID). Patients were randomized to treatment with *Wellbutrin XL* or *Wellbutrin* for 14 days, followed by a 14 day washout period and then switched to the alternative treatment. Bioequivalence was demonstrated for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion and erythrohydrobupropion). In a study of similar design, *Wellbutrin XL* 300 mg QAM and *Wellbutrin SR* 150 mg given twice daily (BID) demonstrated bioequivalence to bupropion and its metabolites in 49 healthy volunteers (4). Bioequivalence has previously been demonstrated between the sustained-release formulation and the immediate-release formulation of bupropion for peak plasma concentration and AUC for bupropion and the

3 metabolites (5). Table 1 describes the population average pharmacokinetic characteristics of bupropion formulations based on pharmacokinetic modeling of data obtained from the 2 pharmacokinetic studies previously described (6).

**Table 1. Population Average Pharmacokinetic Characteristics of Bupropion Formulations (300 mg total daily dose)**

Characteristic	<i>Wellbutrin</i> (100 mg TID) (6)	<i>Wellbutrin SR</i> (150 mg BID) (4,6)	<i>Wellbutrin XL</i> (300 mg QAM) (4,6)
t <sub>max</sub> (bupropion)	1.5 hours	2.5 hours	5 hours
t <sub>max</sub> (metabolites*)	3-4 hours	5-6 hours	7-8 hours
Single-dose C <sub>max</sub> (bupropion)	102 ng/mL	78.53 ng/mL	99.7 ng/mL
Steady-state C <sub>max</sub> (bupropion)	144.12 ng/mL	111.72 ng/mL	119.17 ng/mL
Steady-state C <sub>min</sub> (bupropion)	29.75 ng/mL	26.03 ng/mL	23.12 ng/mL
AUC	1740 ng.h/mL	1483 ng.h/mL	1382 ng.h/mL

\*metabolites include hydroxybupropion, threohydrobupropion and erythrohydrobupropion

t<sub>max</sub>: time to reach peak plasma concentration

C<sub>max</sub>: maximum plasma concentration after dosing

C<sub>min</sub>: concentration at the end of a dosing interval during multiple dosing

AUC: Area Under the Concentration-Time Curve

TID: three times daily; BID: twice daily; QAM: every morning

Because of the slower rate of release of bupropion from *Wellbutrin XL* versus *Wellbutrin* and *Wellbutrin SR* tablets, the time to peak plasma concentration (t<sub>max</sub>) of bupropion is prolonged, and the decline in plasma concentrations of bupropion is less pronounced with *Wellbutrin XL*.

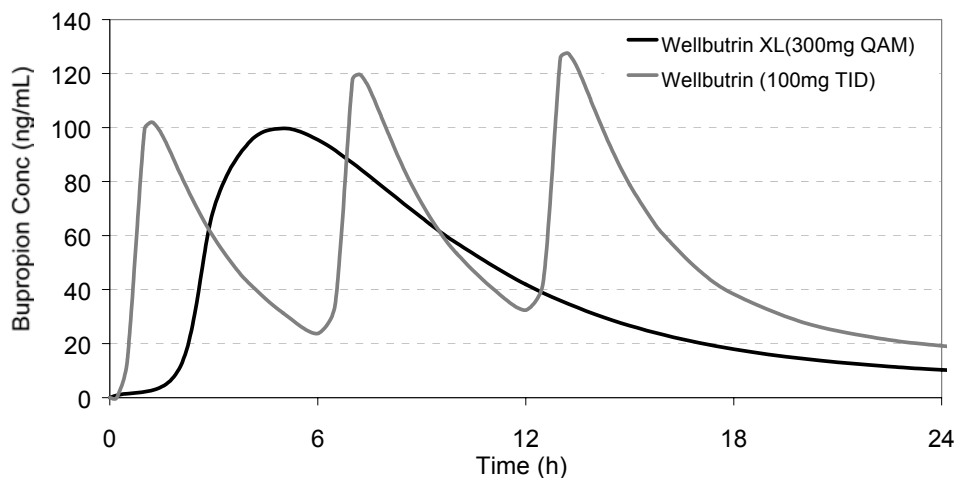
Subjects completing pharmacokinetic studies with *Wellbutrin XL* tolerated the 300 mg extended-release formulation as a single daily dose and reported no new or unexpected adverse events (3).

Based on previously demonstrated linear pharmacokinetics of bupropion and its metabolites following chronic administration and an additional pharmacokinetic evaluation in healthy volunteers, the 150 mg and 300 mg *Wellbutrin XL* tablets are considered dose proportional (3). These findings also support the combination of 3 150 mg *Wellbutrin XL* tablets or one 150 mg *Wellbutrin XL* tablet plus one 300 mg *Wellbutrin XL* tablets to achieve the maximum recommended single dose of 450 mg/day.

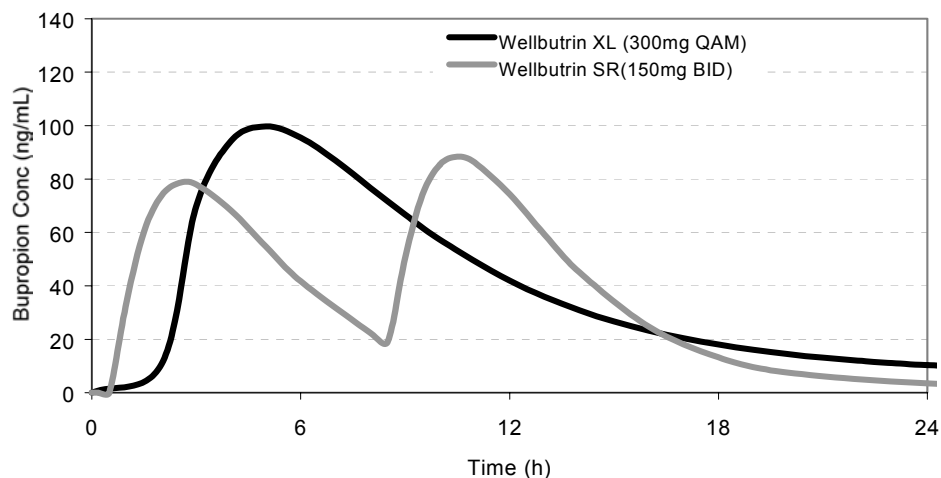
#### Single-dose Pharmacokinetics of *Wellbutrin XL*

Single-dose population average concentration-time curves for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin* 100 mg TID or *Wellbutrin SR* 150 mg BID are depicted in Figures 1 and 2, respectively.

**Figure 1. Single-Dose Population Average Pharmacokinetics for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin* 100 mg TID (6)**



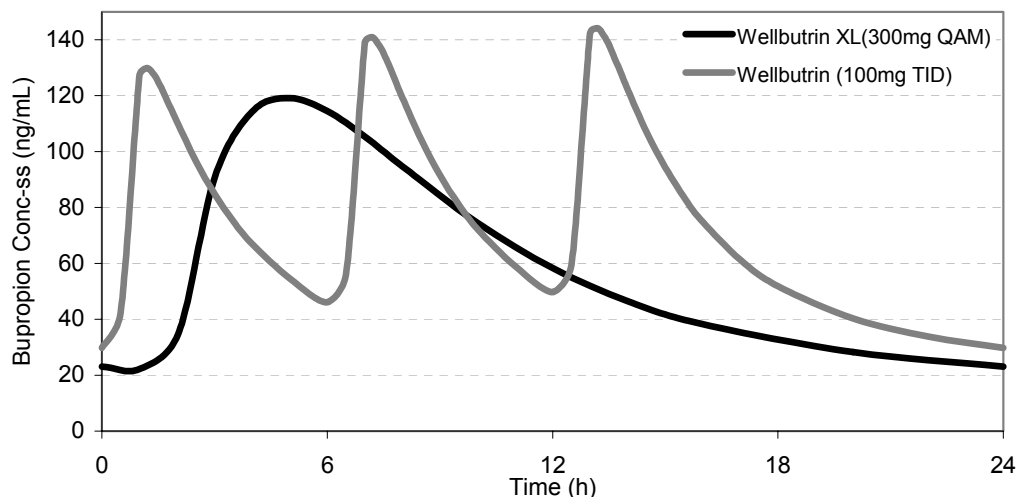
**Figure 2. Single-Dose Population Average Pharmacokinetics for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin SR* 150 mg BID (6)**



*Steady-state Pharmacokinetics of Wellbutrin XL 300 mg QAM*

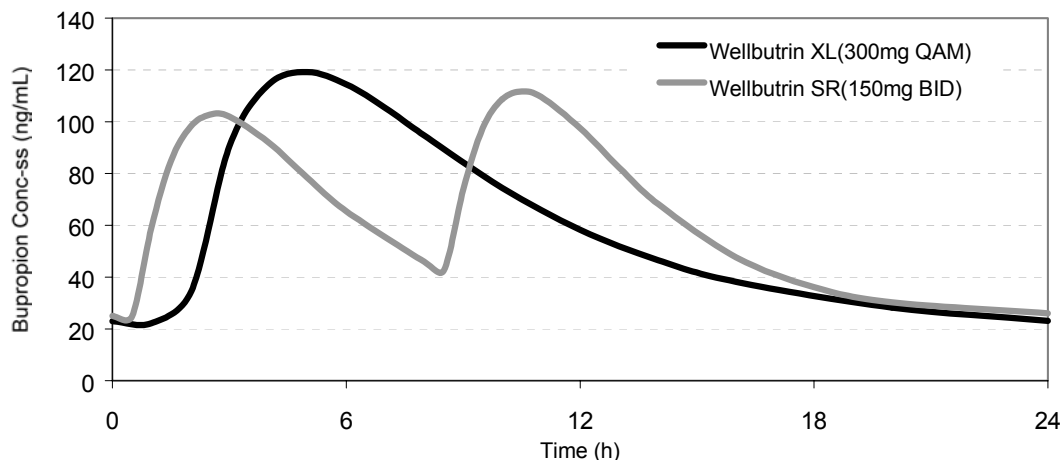
Figures 3 and 4 describe steady-state population average concentration-time curves for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin* 100 mg TID or *Wellbutrin SR* 150 mg BID, respectively (6).

**Figure 3. Steady-State Population Average Pharmacokinetics for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin* 100 mg TID (6)**



At steady-state, peak plasma concentrations of bupropion following oral administration of *Wellbutrin XL* 300 mg once daily are approximately 17% lower than those achieved following dosing with *Wellbutrin* 100 mg TID with the administration of a higher individual dose of *Wellbutrin XL* (300 mg) compared with *Wellbutrin* (100 mg) (119.17 ng/mL versus 144.12 ng/mL).

**Figure 4. Steady-State Population Average Pharmacokinetics for *Wellbutrin XL* 300 mg QAM versus *Wellbutrin SR* 150 mg BID (6)**



Peak steady-state plasma concentrations with *Wellbutrin XL* 300 mg once daily are approximately 7% higher than those achieved with *Wellbutrin SR* 150 mg BID (119.17 ng/mL versus 111.72 ng/mL) with the administration of a higher individual dose of *Wellbutrin XL* (300 mg) compared with *Wellbutrin SR* (150 mg). If *Wellbutrin SR* 150 mg is taken at 8 AM and 4 PM and *Wellbutrin XL* 300 mg is taken at 8 AM, steady-state bedtime plasma levels of *Wellbutrin SR* at 10 PM are 47% higher than those seen with *Wellbutrin XL* (46.53 ng/mL versus 68.28 ng/mL).

With this same dosing regimen, steady-state population average trough plasma concentrations with *Wellbutrin XL* 300 mg QAM are comparable to those seen with *Wellbutrin* 100 mg TID and *Wellbutrin SR* 150 mg BID. However, according to PET studies in humans which evaluated the binding of bupropion to the dopamine reuptake transporter, fluctuation in plasma concentrations of the parent drug does not reflect fluctuation in dopamine reuptake transporter occupancy (7). This may be due to slow diffusion into and out of the brain, the contribution of bupropion metabolites (which fluctuate less than the parent drug), or slow dissociation of bupropion and/or its metabolites from the dopamine transporter. Regardless of the mechanism, data suggest that differences in  $C_{min}$  between various bupropion formulations will not result in a significant reduction in dopamine reuptake transporter occupancy in the brain.

#### *Steady-state Pharmacokinetics of Wellbutrin XL 450 mg QAM*

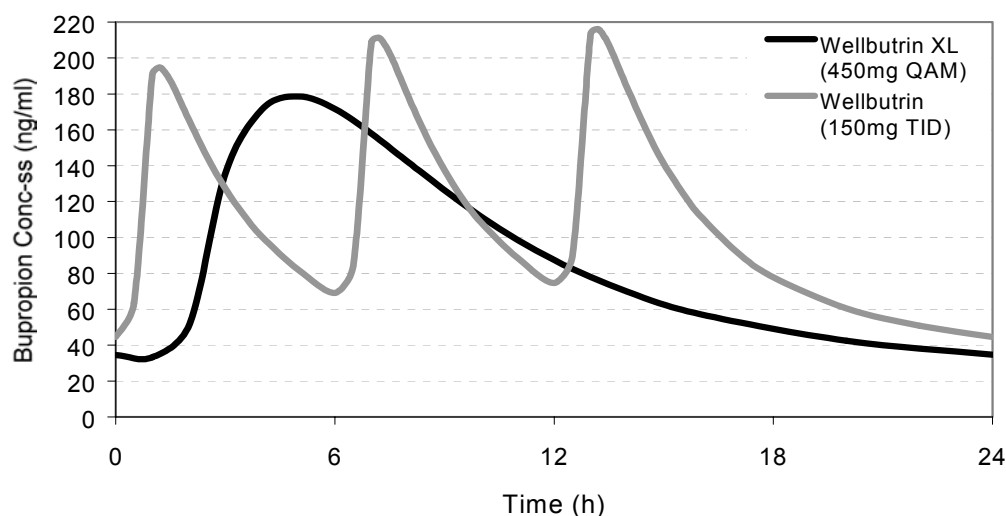
Pharmacokinetic modeling of data derived from 2 pharmacokinetic studies (*Wellbutrin XL* 300 mg QAM versus *Wellbutrin* 100 mg TID and *Wellbutrin XL* 300 mg QAM versus *Wellbutrin SR* 150 mg BID) was conducted to predict the population average pharmacokinetics of various doses of bupropion formulations (6). The population average pharmacokinetics of *Wellbutrin XL* 450 mg QAM versus *Wellbutrin* 150 mg TID or *Wellbutrin SR* 200 mg BID are described in Table 2 and Figures 5 and 6, respectively.

**Table 2. Population Average Pharmacokinetic Characteristics of Bupropion Formulations (400-450 mg total daily dose) (6)**

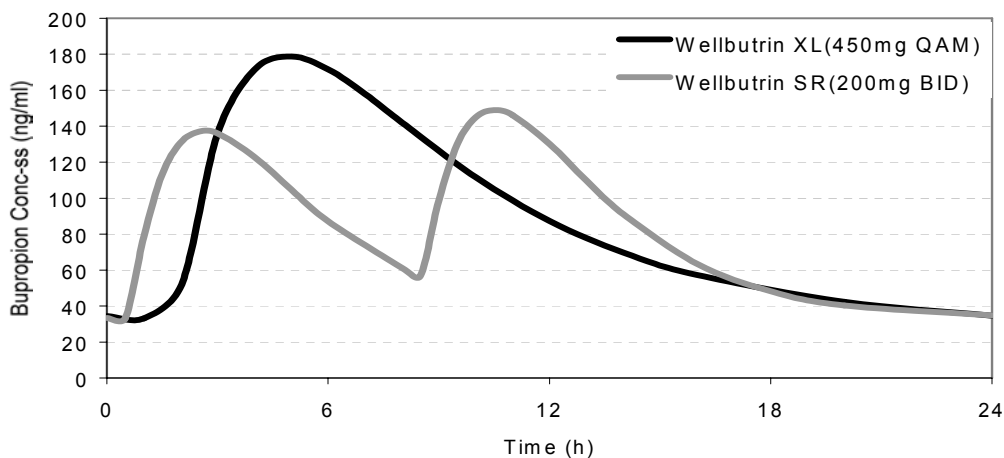
Characteristic	<i>Wellbutrin</i> (150 mg TID)	<i>Wellbutrin SR</i> (200 mg BID)	<i>Wellbutrin XL</i> (450 mg QAM)
Single-dose $C_{max}$ (bupropion)	152.99 ng/mL	104.71ng/mL	149.56 ng/mL
Steady-state $C_{max}$ (bupropion)	216.18 ng/mL	148.95 ng/mL	178.67 ng/mL
Steady-state $C_{min}$ (bupropion)	44.63 ng/mL	34.7ng/mL	34.63 ng/mL
AUC	2610 ng.h/mL	1978 ng.h/mL	2072 ng.h/mL

$C_{max}$ : maximum plasma concentration after dosing  
 $C_{min}$ : concentration at the end of a dosing interval during multiple dosing  
AUC: Area Under the Concentration-Time Curve  
TID: three times daily; BID: twice daily; QAM: every morning

**Figure 5. Steady-State Population Average Pharmacokinetics for *Wellbutrin XL* 450 mg versus *Wellbutrin* 150 mg TID (6)**



**Figure 6. Steady-State Population Average Pharmacokinetics for *Wellbutrin XL* 450 mg versus *Wellbutrin SR* 200 mg BID (6)**



**Pharmacokinetic Parameters**

Additional general disposition and pharmacokinetic properties of *Wellbutrin XL* are summarized in Table 3.

**Table 3. Pharmacokinetic Properties of Bupropion after Administration of *Wellbutrin XL***

Property	Comments
<b>Absorption</b>	<ul style="list-style-type: none"> <li>• At equal doses, the amount of bupropion absorbed from <i>Wellbutrin XL</i> is the same as from <i>Wellbutrin</i> and <i>Wellbutrin SR</i> (3).</li> <li>• The absolute bioavailability of bupropion has not been determined in man because an intravenous formulation of bupropion for human use is not available (8). However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact (9).</li> <li>• According to pharmacokinetic studies in healthy volunteers, bupropion and its metabolites appear to be absorbed throughout the gastrointestinal tract, although absorption diminishes near the cecum/colon (10).</li> <li>• The effects of food on the pharmacokinetic profile of <i>Wellbutrin XL</i> were studied in subjects who received a single dose of <i>Wellbutrin XL</i> with food and under fasted conditions. This study concluded that <i>Wellbutrin XL</i> may be given without regard to meals (2).</li> </ul>
<b>Distribution</b>	<ul style="list-style-type: none"> <li>• <i>In vitro</i> tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL (2,11). The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.</li> <li>• Mean apparent oral clearance: 200 L/hr</li> <li>• Volume of distribution: 700 L</li> </ul>
<b>Metabolism</b>	<ul style="list-style-type: none"> <li>• Bupropion is extensively metabolized in humans.</li> <li>• Three metabolites have been shown to be active: <ul style="list-style-type: none"> <li>– Hydroxybupropion is formed via hydroxylation of the <i>tert</i>-butyl group of bupropion</li> <li>– Threohydrobupropion and erythrohydrobupropion (amino-alcohol isomers) are formed via reduction of the carbonyl group</li> <li>– The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.</li> </ul> </li> <li>• Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite.</li> <li>• <i>In vitro</i> findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion. To a lesser extent, CYP1A2, 2A6, 2C9, 2E1 and 3A4 may contribute to the metabolism of bupropion (12).</li> <li>• Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by CYP2B6.</li> <li>• Although bupropion is not metabolized by CYP2D6, it is an inhibitor of CYP2D6. There is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme.</li> <li>• Cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.</li> <li>• Mean <math>t_{1/2}</math> (<math>\pm</math>SD) after chronic dosing: bupropion 21 (<math>\pm</math>9) hours, hydroxybupropion 20 (<math>\pm</math>5) hours, erythrohydrobupropion 33 (<math>\pm</math>10) hours, threohydrobupropion 37 (<math>\pm</math>13) hours.</li> <li>• The initial rapid, non-linear decline in plasma concentrations of bupropion observed in Figures 3 and 4 may be explained by a multicompartment model. Bupropion distributes from the plasma at various rates into different tissue compartments, such as the brain. After equilibration with these other compartments, the plasma concentration-time curve of bupropion resumes first-order elimination (13).</li> <li>• Approximate <math>t_{max}</math>: bupropion (5 hours), hydroxybupropion (7 hours), and</li> </ul>

Property	Comments
	<p>threohydrobupropion and erythrohydrobupropion (8 hours).</p> <ul style="list-style-type: none"> <li>• AUC of metabolites at steady state relative to bupropion: hydroxybupropion-13 times bupropion, erythrohydrobupropion-1.4 times bupropion, threohydrobupropion-7 times bupropion.</li> <li>• Steady-state plasma concentrations of bupropion are reached within 8 days.</li> <li>• Bupropion and its metabolites exhibit linear kinetics following single doses and chronic administration of <i>Wellbutrin</i> 300 to 450 mg/day.</li> <li>• Bupropion has been shown to induce its own metabolism in 3 animal species (mice, rats and dogs) following subchronic administration (14). However, there was no evidence of bupropion autoinduction in healthy volunteers who received up to 450 mg daily for 14 days (15).</li> </ul>
<b>Elimination</b>	<ul style="list-style-type: none"> <li>• Following oral administration of 200 mg of <sup>14</sup>C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.</li> </ul>
<p><math>C_{max}</math>: maximum plasma concentration after dosing  <math>t_{max}</math>: time to reach peak plasma concentration  <math>AUC_{0-\tau}</math>: area under the concentration-time curve from time zero to time of dosing interval (<math>\tau=24</math> hours)</p>	<p><math>C_{min}</math>: concentration at the end of a dosing interval during multiple dosing  <math>t_{1/2}</math>: half-life</p>

**REV0405**

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**Enclosure: Prescribing Information for *Wellbutrin XL***