ORTHO-McNEIL

August 29, 2005 9559 '05 AUG 29 P3:09

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

Prompted by the current re-examination of technical, scientific, and clinical data for DITROPAN XL® (oxybutynin chloride) Extended-Release Tablets and other oxybutynin dosage forms, Ortho Urology, a unit of Ortho-McNeil Pharmaceutical, Inc, submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 CFR § 10.30. Ortho Urology requests that the Commissioner of the Food and Drug Administration (FDA) require that standard bioequivalence criteria be applied separately to oxybutynin and its active metabolite, desethyloxybutynin, to ensure that approved generic versions of DITROPAN XL are both bioequivalent and clinically equivalent to the innovator product.

A. ACTION REQUESTED

Ortho Urology supports FDA's Office of Generic Drugs in the approval of therapeutically equivalent drug products. Ortho Urology has no objection to the consideration of a generic version of DITROPAN XL as long as FDA ensures that the generic version exhibits pharmacokinetic profiles of oxybutynin and desethyloxybutynin comparable to DITROPAN XL, and can be found to be clinically equivalent. This petition presents scientific reasons to support the conclusion that a bioequivalence determination between oxybutynin extended-release products, which have been deemed pharmaceutically equivalent or as alternative dosage forms, may not predict clinical and safety effects based solely on plasma concentrations of oxybutynin.

In this petition, Ortho Urology provides scientific and clinical evidence that oxybutynin's major metabolite, desethyloxybutynin, is formed by presystemic gut-wall metabolism and that this metabolite contributes meaningfully to the safety and efficacy profile, so it should be considered in assessing bioequivalence. In addition, Ortho Urology presents supportive scientific and clinical data toward this end demonstrating that oxybutynin, a chiral drug, exhibits nonlinear absorption, that its R- and S-enantiomers exhibit different

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pharmacodynamic and pharmacokinetic characteristics, and that the primary safety and efficacy activity resides with the R-enantiomers of both oxybutynin and desethyloxybutynin.

Clinical differences among oxybutynin products can be mainly attributed to the relative concentrations of metabolite to parent that are influenced by various dosage form technologies, immediate- and extended-release rates, and residence times in specific regions of the gastrointestinal tract. These clinical differences include the expression and tolerability of untoward anticholinergic effects and adherence to treatment, especially in the elderly population. The overall therapeutic management of overactive bladder can be affected, because patients are commonly titrated to the most effective dose of oxybutynin, which is a balance between the improvement of symptoms and tolerability of adverse effects.

ALZA Corporation developed DITROPAN XL using its OROS® delivery technology, and recognized the importance of delineating the pattern of systemic exposures for the R and S-enantiomers of oxybutynin and desethyloxybutynin as they relate to the safety and efficacy profile. ALZA assessed the four active moieties[1] in all pivotal pharmacokinetic, bioavailability, and bioequivalence studies submitted in NDA 20-897, and pertinent information is provided in the product labeling. Consistent with this standard, bioequivalence of the clinical and commercial OROS formulations was established by applying FDA's bioequivalence metrics and confidence interval criteria *a priori* to the R- and S-enantiomers of both the parent drug and active metabolite.[2]

For extended-release oxybutynin products, bioequivalence decisions based solely on oxybutynin plasma concentrations are insufficient without consideration of the metabolite and the inherent stereoselective differences of both active moieties. This can lead to the inappropriate approval of generic products deemed bioequivalent, which ultimately prove to have very different adverse effect and safety profiles once in widespread use for overactive bladder. Ortho Urology, therefore, requests that FDA require bioequivalence criteria be applied separately to both oxybutynin and desethyloxybutynin, rather than only measure the active metabolite[3], to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin products. Moreover, application to the two active moieties of oxybutynin should be required in bioequivalence studies conducted under both fasting and fed conditions.

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[1] 21 CFR § 320.24(b)(1)(i).
[2] NDA 20-897, ALZA Clinical Study Report C-97-015-01, 12/1997.
[3] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003, p 17.

B. STATEMENT OF GROUNDS

I. EXECUTIVE SUMMARY

Overactive bladder is a chronic condition that affects an estimated 33 million people in the United States. It is most prevalent among the elderly and involves symptoms of urinary frequency and urgency with or without urge incontinence. About one half of the affected population has urgency with urinary incontinence, which can have notable consequences for the health and emotional well-being of sufferers. Oxybutynin, an anticholinergic agent and smooth muscle relaxant, is a first-line treatment for overactive bladder. DITROPAN XL is a once-daily extended-release form of oxybutynin that utilizes the OROS delivery system to deliver the drug continuously over a 24-hour period.

Oxybutynin and its active metabolite, desethyloxybutynin, are about equipotent in their anticholinergic effects that control symptoms of overactive bladder. They both contribute to expected dose-related antimuscarinic adverse effects, such as dry mouth, nausea, constipation, and somnolence. These adverse effects can be severe enough to render therapy intolerable to some patients and limit their ability to continue without either lowering to a less effective dose or stopping therapy. However, desethyloxybutynin contributes more substantially to the dose-related adverse effects, so the overall balance between the tolerability and efficacy of therapy is related to the relative systemic concentrations of metabolite to parent.

DITROPAN XL partially bypasses first-pass metabolism due to its release-rate profile and gastrointestinal transit time. The resulting lower metabolite-to-parent concentration ratio renders DITROPAN XL therapeutically distinct from other oral oxybutynin products. Data from published pharmacokinetic-pharmacodynamic studies show directly that higher metabolite concentrations are associated with less saliva production and more severe dry mouth. Patients in clinical trials also report less untoward anticholinergic effects in general for oxybutynin products that produce less metabolite. Because overactive bladder is a chronic condition, drug therapy is most successful if it can be sufficiently tolerated by patients needing long-term treatment.

- **For Extended-Release Oxybutynin Products, Bioequivalence Decisions Based Solely on Oxybutynin Plasma Concentrations Are Insufficient**

Bioequivalence determinations are generally based on AUC, AUC_{INF}, and C_{MAX} of the administered active ingredient and/or active moieties. For this petition, only AUC_{INF} and C_{MAX} comparisons are discussed for simplicity, because it is assumed that AUC_{INF} is determined as the summation of area computed to the last quantifiable plasma

concentration and area extrapolated to infinity, and that blood is sampled for at least three half-lives of the active moiety. AUCINF represents the total systemic exposure of a dose.

Collectively, scientific and clinical study data within this petition show that the OROS drug delivery technology of DITROPAN XL with its release-rate profile contributes uniquely to differences in the relative concentrations of desethyloxybutynin and oxybutynin. If bioequivalence of only oxybutynin is considered, extended-release products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent. To prevent this, the bioequivalence metrics (log-transformed AUCINF and CMAX) and criteria (90% confidence limits from 80.0% to 125.0%) should be applied to both oxybutynin and desethyloxybutynin in a single-dose study in healthy *fasting* volunteers. Equivalence of each active moiety verifies that the overall pattern of systemic exposures is similar between DITROPAN XL and a generic version. Therefore, the balance between efficacy, safety, and tolerability to treatment would also be similar, which is expected by patients, caregivers, and health professionals when products are substituted.

- **Desethyloxybutynin, Formed by Presystemic Gut-Wall Metabolism, Contributes Meaningfully to Safety and Efficacy of Oxybutynin**

Oxybutynin is mainly oxidized by the cytochrome P450 3A4 (CYP3A4) isoenzyme into the active desethyloxybutynin metabolite. The upper small intestine serves as the major site for intestinal CYP3A-mediated first-pass metabolism of oxybutynin. Because desethyloxybutynin exhibits antimuscarinic activity similar to that of parent drug, but has significantly higher affinity to the salivary gland for example, the rate and extent of its formation will influence the time course and amplitude of both clinical and untoward anticholinergic effects, such as moderate-to-severe dry mouth.

FDA's guidance recommends[4] that if a metabolite is formed as a result of presystemic gut-wall metabolism and that it contributes meaningfully to safety and/or efficacy, both the parent and metabolite should be measured in a bioequivalence study. However, FDA indicates that bioequivalence criteria would be applied to only the parent. Ortho Urology asserts that bioequivalence criteria should be applied to the active metabolite as well because of the dominant role it has in the safety and efficacy of oxybutynin.

Published studies show that DITROPAN XL extended-release tablets have lower ratios of metabolite-to-parent concentrations than the immediate-release tablet and an extend-release tablet that incorporates a swelling erodible matrix. Compared with these two types of oral products, less drug is released by DITROPAN XL in the upper small intestine and

[4] Ibid 3, p 18.

more in the colon, thus avoiding some presystemic metabolism. Other factors that alter gastrointestinal transit time, like food, also change the metabolite-to-parent concentration ratios for some oral oxybutynin products, including the extended-release erodible matrix tablet. Importantly, the OROS delivery technology of DITROPAN XL is not affected by food. Because of complex interactions among drug delivery technology, food, gastrointestinal transit time, and site-specific metabolism, bioequivalence criteria should be applied to the four active moieties of oxybutynin in the *food-effect* single-dose study in healthy volunteers. This is also essential in the evaluation of extended-release oxybutynin products to ensure therapeutic equivalence.

- **Stereoselective Metabolism and Pharmacologic Activities Support Application of Bioequivalence Criteria to Oxybutynin and Its Active Metabolite**

Oxybutynin and active metabolite, desethyloxybutynin, are approximately equipotent in their anticholinergic effects on human detrusor muscle of the bladder, but the metabolite is more potent than the parent in anticholinergic effects on the salivary gland. In addition, oxybutynin undergoes stereoselective metabolism in which preferential oxidation of R-oxybutynin leads to its lower bioavailability compared with the S-enantiomer, and to significantly higher systemic exposure of R-desethyloxybutynin. This is important to consider because the main pharmacologic activities reside with the R-enantiomers. Pharmacokinetic-pharmacodynamic studies also show that differences in the metabolite-to-parent concentration ratios of the R-enantiomers among oxybutynin products cause varying expression of untoward anticholinergic effects.

Even at the same daily dose, bioavailabilities of R- and S-enantiomers of the parent and active metabolite are often markedly different because of differences in drug release rates among immediate- and extended-release oxybutynin products coupled with site-specific gut-wall metabolism. Therefore, applying bioequivalence criteria separately to oxybutynin and desethyloxybutynin would be sufficiently sensitive to such formulation and release rate effects that may alter desired patient outcomes in the management of overactive bladder. If bioequivalence of only oxybutynin is considered, extended-release products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent. Therefore, Ortho Urology requests that FDA require that bioequivalence criteria be applied to the two active moieties, oxybutynin and desethyloxybutynin, to ensure clinical equivalence for extended-release oxybutynin products.

II. THERAPEUTIC IMPLICATIONS FOR OVERACTIVE BLADDER

A. Overactive Bladder Prevalence and Impact on Patients

Overactive bladder is a chronic condition involving symptoms of urinary frequency and urgency, with or without urge incontinence. Overactive bladder is estimated to affect over 33 million people[5] in the United States, with urinary incontinence affecting 17 million[6] of this population. The prevalence of overactive bladder increases with age in both men and women[7], and is markedly high among nursing home residents, with some estimates of urinary incontinence at >50% in this population.[8]

Symptoms of overactive bladder have a substantial negative impact on personal quality of life and general public health. Patients with overactive bladder suffer from decreased quality of sleep,[9] a higher risk of urinary tract infections,[10] and a heightened risk of falls and fractures, possibly related to hurried nocturnal voiding.[11,12] They also frequently endure social isolation and decreased participation in social activities to avoid potentially embarrassing situations,[13] effectively becoming prisoners to the disorder. Symptoms of overactive bladder can be particularly debilitating in the geriatric population. Elderly patients with urinary incontinence are twice as likely to feel depressed and have worse perceived health compared with age-matched controls.[14] Urinary incontinence in the elderly also is reported to be a risk factor for hospitalization and admission into long-term care.[15]

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[5] Stewart WF, Van Rooyen JB, Cundiff GW, *et al.* Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20(6):327-36.

[6] Hu TW, Wagner TD, Bentkover JD, *et al.* Costs of urinary incontinence and overactive bladder in the US: A comparative study. *Urology* 2004;63:461-5.

[7] Ibid. 5.

[8] Dey AN. Characteristics of elderly nursing home residents: data from the 1995 National Nursing Home Survey. *Adv Data* 1997;289:1-8.

[9] Ibid. 5.

[10] Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy* 2005;25(4):511-19.

[11] Brown JS, Vittinghoff E, Wyman JF, *et al.* Urinary incontinence: Does it increase risk for falls and fractures? *JAGS* 2000; 48: 721-725.

[12] Ibid. 10.

[13] Grimby A, Milsom I, Mulander U, *et al.* The influence of urinary incontinence on the quality of life in elderly women. *Age Ageing* 1993;3:82-9.

[14] Ko Y, Lin SJ, Salmon JW, Bron MS. The impact of urinary incontinence on quality of life of the elderly. *Am J Manag Care* 2005;11:S103-S111.

[15] Thom DH, Haan MN, Van Den Eden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. *Age Ageing* 1997; 26: 367-374.

The estimated overall economic costs ($12.02 billion in 2000) are comparable to those of osteoporosis and gynecologic or breast cancer.[16,17] These costs will likely increase considerably over the next 30 years as the demand for resources and services related to overactive bladder rises with the aging population.

B. Oxybutynin Benefits for Overactive Bladder

The symptoms of urgency, frequency, and possible urinary incontinence in overactive bladder result from detrusor muscle hyperactivity. Anticholinergic medications are a common pharmacotherapy for overactive bladder, as they control the intensity of detrusor muscle contractions that are mediated by cholinergic pathways. Oxybutynin is an antispasmodic, antimuscarinic agent approved for the treatment of symptoms of bladder instability.[18] It is one of the most studied anticholinergic compounds available in the United States. The antimuscarinic and antispasmodic activities of oxybutynin increase bladder capacity, decrease uninhibited bladder spasms, and delay the initial desire to void.

C. Balancing Treatment Effectiveness and Tolerability

DITROPAN XL is an extended-release form of oxybutynin that utilizes the OROS delivery system to deliver oxybutynin continuously over a 24-hour period.[19] This product allows for effective management of symptoms with once-daily dosing, without the fluctuations between peak and trough plasma concentrations associated with short-acting, immediate-release oxybutynin. Six doses (5, 10, 15, 20, 25, and 30 mg) are FDA-approved so that patients can be started with the recommended dose of 5 or 10 mg once daily, and be titrated to an optimal effective and tolerable dose.

Many anticholinergic treatments for overactive bladder, including oxybutynin, cause expected dose-related antimuscarinic adverse effects such as dry mouth, nausea, constipation, and somnolence.[20] These adverse effects can reduce drug tolerability, limit titration to effective doses, and lead to poor adherence and treatment discontinuation. [21] Such tolerability issues may be particularly problematic for elderly patients sensitive to

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[16] Hu TW, Wagner TH, Bentkover JD, *et al.* Estimated economic costs of overactive bladder in the United States. *Urology* 2003;61:1123-8.

[17] Ibid. 5.

[18] DITROPAN® [Package Insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2003.

[19] DITROPAN XL® [Package Insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2004.

[20] Ibid. 19.

[21] Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder. *Urology* 2000;55(suppl 5A):33-46.

central nervous system actions of anticholinergic drugs, and for patients taking other medications with the potential to interact with anticholinergics.[22] In these patients, the greater susceptibility to central nervous system effects such as dizziness, somnolence and cognitive impairment represents a significant safety concern, as decreased alertness could lead to an increased risk for accidents. Notably, clinical studies comparing DITROPAN XL with equally effective doses of immediate-release oxybutynin have reported that DITROPAN XL is associated with fewer adverse events,[23,24] less suppression of salivary production,[25,26] lower study discontinuation rates,[27,28,29,30,31,32] and a wider therapeutic index for efficacy versus dry mouth.[33] Also, in a recent update to the *Beers List* of medications deemed potentially inappropriate for use in the elderly, the listing for oxybutynin was modified to exclude DITROPAN XL, as the independent expert panel believed this formulation had fewer side effects than the immediate-release formulation.[34]

The reduced adverse events in patients taking DITROPAN XL are due to its unique pharmacokinetic profiles of oxybutynin and active metabolite that are imparted by the drug release characteristics of the OROS delivery system. In fact, reductions in adverse events relative to immediate-release oxybutynin were not observed in studies of another extended-release oxybutynin product, CYSTRIN CR®, when equally effective dosing regimens were

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[22] Scheife R, Takeda, M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clinical Therapeutics* 2005;27:144-153.

[23] Anderson RU, Mobley D, Blank B, *et al.* Once-daily controlled- versus immediate-release oxybutynin chloride for urge urinary incontinence. *J Urol* 1999; 161:1809-12.

[24] Versi E, Appel R, Mobley D, *et al.* Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. *Obstet Gynecol* 2000;95(5):718-21.

[25] Chancellor MB, Appell RA, Sathyan G, *et al.* A comparison of the effects on salivary output of oxybutynin chloride and tolterodine tartrate. *Clin Ther* 2001;23:753-60.

[26] Sathyan G, Chancellor MB, Gupta SK. Effect of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol* 2001;52:409-417.

[27] Ibid. 19.

[28] NDA20-896, Integrated Summary of Safety, 12/1997

[29] Diokno A, Sand P, Labasky R, *et al.* Long-term safety of extended-release oxybutynin chloride in a community-dwelling population of participants with overactive bladder. *Int Urol Nephrol* 2002;34:43-9.

[30] Boccuzzi SJ, Le TK, Wogen J, Williamson T. Utilization patterns associated with tolterodine immediate release versus oxybutynin in the management of urinary incontinence [abstract #274]. *Value Health* 2002;5:274.

[31] Shaya FT, Blume S, Gu A, et al. Persistence With overactive bladder pharmacotherapy in a medicaid population. *Am J Manag Care* 2005;11:S121-S129.

[32] Varadharajan S, Jumadilova Z, Girase P, Ollendorf DA. Economic impact of extended-release tolterodine versus immediate- and exended-release oxybutynin among commercially insured persons with overactive bladder. *Am J Managed Care* 2005;11:S140-149

[33] Gupta SK, Sathyan G, Lindemulder EA, *et al.* Quantitative characterization of therapeutic index: Application of mixed-effects modeling to evaluate oxybutynin dose-efficacy and dose-side effect relationships. *Clin Pharmacol Ther* 1999;65:672-84.

[34] Fick DM, Cooper JW, Wade WE, *et al.* Updating the Beers criteria for potentially inappropriate medication use in older adults. *Arch Int Med* 2003;163:2716-24.

compared.[35,36] The current petition provides data that the release-rate profile of oxybutynin determined by the OROS delivery system results in lower systemic concentrations of metabolite relative to the parent due to the partial bypass of first-pass metabolism in the upper small intestine. As a consequence, antimuscarinic adverse effects, primarily caused by the metabolite, are reduced.

[35] Birns J, Lukkari E, Malone-Lee J. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU Internat* 2000;85:793-8.

[36] Nilsson CG, Lukkari E, Haarala M, *et al.* Comparison of a 10 mg controlled release oxybutynin tablet with a 5 mg oxybutynin tablet in urge incontinent patients. *Neurourol Urodyn* 1997;16:533-42.

III. VARYING DELIVERY FEATURES OF ORAL OXYBUTYNIN PRODUCTS

A. Immediate-Release Oral Oxybutynin Tablets and Syrup

Immediate-release oral forms of oxybutynin are currently available as branded (DITROPAN®) and generic tablets (5 mg) or syrup solutions (5 mg / 5 mL) containing R,S (racemic) oxybutynin chloride.[37] The compressed tablets disintegrate quickly upon ingestion, so oxybutynin is rapidly absorbed, achieving CMAX within an hour. Plasma concentrations then decrease with an effective half-life of approximately two to three hours, which contributes to the need for dosing up to four times daily. The absolute bioavailability of oxybutynin is reported to be only about 6% (range = 1.6% to 10.9%) for both tablet and syrup.

B. CYSTRIN CR® (Controlled-Release Matrix Tablets)

CYSTRIN CR is a once-daily, extended-release form of oxybutynin, currently available only in Finland, that uses the TIMERx® controlled-release delivery system[38]. The TIMERx delivery system is a hydrophilic matrix comprised of a heteropolysaccharide, a galactomannan, and dextrose. These components form a tight binder gel with a slowly eroding core that expands in an aqueous environment and releases R,S (racemic) oxybutynin chloride at a controlled rate that depends on the rate of water penetration into the matrix. As water penetrates the outer layers, the tablet begins to swell and slowly break down, releasing some of the drug and slightly reducing the center drug core. Most of the matrix erodes within 21 hours, and the unwetted core is reduced to a very small percentage of the tablet. The oxybutynin from CYSTRIN CR reaches maximal plasma concentrations in approximately two hours, and then declines gradually over 24 hours.[39]

C. DITROPAN XL (OROS Extended-Release Tablets)

DITROPAN XL is a once-daily, extended-release product that uses the OROS osmotic delivery system to release racemic oxybutynin chloride at a controlled rate over approximately 24 hours.[40] The OROS system comprises an osmotically active bilayer core surrounded by a semipermeable membrane (Figure 1). The bilayer core consists of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. In the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand, pushing

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[37] Ibid. 18.
[38] http://media.corporate-ir.net/media_files/irol/90/90346/reports/penwest2004ar.pdf accessed 8/22/05.
[39] Ibid. 36.
[40] Ibid. 19.

the drug suspension out through a precision laser-drilled orifice on the drug-layer side of the tablet. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery into the gastrointestinal lumen independent of pH or gastrointestinal motility. Since the osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract remains constant, drug delivery remains essentially constant. The biologically inert components of the non-disintegrating tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

Each DITROPAN XL tablet contains 5, 10, or 15 mg of oxybutynin chloride formulated as a racemic mixture of 49% R- and 51% S-enantiomers. Chemical analyses indicate that the ratio of the two enantiomers does not change during the manufacturing process of the drug product. Following the first dose, oxybutynin enantiomer plasma concentrations rise for four to six hours; thereafter, steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with immediate-release oxybutynin.

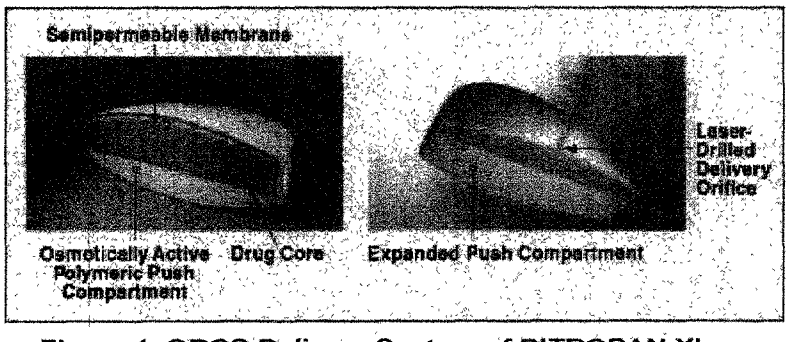

Figure 1. OROS Delivery System of DITROPAN XL.

IV. REQUEST FOR BIOEQUIVALENCE CRITERIA BE APPLIED SEPARATELY TO OXYBUTYNIN AND DESETHYLOXYBUTYNIN TO ENSURE THERAPEUTIC EQUIVALENCE

A. Statement of the Issue and Requested Action

FDA regulations define bioequivalence as the "absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[41] Preferably, the rate and extent of drug absorption is measured by means of an *in vivo* study in humans in which drug concentration in blood, plasma, or another appropriate biological fluid is measured as a function of time.[42] According to regulatory guidance, blood should be sampled with sufficient frequency to estimate (i) the maximum drug concentration (C_{MAX}) and (ii) the total area under the curve for a period of at least three times the half-life of the drug (AUC).[43]

For the majority of drugs, the active moiety is the administered drug substance and not any of its metabolites. There are exceptions in which the drug substance is inactive (eg, acts as a prodrug) and the major metabolite is active, or both parent and metabolite are active. For chiral drug substances, which are most often administered as the racemic mixture (50% of each stereoisomer), only one enantiomer may be the active moiety or both enantiomers are active but have different pharmacologic effects or potencies. FDA has provided guidance[44] for establishing bioequivalence of drug products with active metabolites and/or with enantiomers having different activities that meaningfully contribute to safety and efficacy.

For oxybutynin, a chiral drug substance, both the parent and metabolite are about equipotent in their anticholinergic effects on human detrusor muscle of the bladder[45], contributing mainly to efficacy, but the metabolite is more potent than the parent in anticholinergic effects on the salivary gland[46], contributing mainly to safety. In addition, the R-enantiomer of oxybutynin has been shown to exert higher anticholinergic activity than the

[41] 21 CFR § 320.1(e).

[42] 21 CFR § 320.24(b)(1)(i)

[43] 21 CFR § 320.26(c).

[44] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003:17-19.

[45] Waldeck K, Larsson B, Andersson KE. Comparison of oxybutynin and its active metabolite, N-desethyloxybutynin, in the human detrusor and parotid gland. *J Urol* 1997;157:1093-7.

[46] Ibid. 45.

S-enantiomer in animal tissues[47], the latter of which contribute more to the spasmolytic effects of oxybutynin.[48] To further complicate the situation, plasma concentration ratios of metabolite-to-parent for each enantiomer depend on the mode of administration (eg, oral, intravesicular, intravenous, and transdermal), pharmaceutical dosage form, and oral release rate as it relates to site-specific metabolism, the drug delivery technology, ingestion with food, and gastrointestinal transit time. Therefore, the pattern of systemic exposures of oxybutynin and desethyloxybutynin, which contribute differently to pharmacologic actions, is critically important to consider in establishing bioequivalence between pharmaceutically equivalent or alternative extended-release oxybutynin products.

For these reasons, Ortho Urology requests that FDA require the application of bioequivalence criteria separately to oxybutynin and desethyloxybutynin in both fasting and food effect studies, which would be sufficiently sensitive to formulation and release rate effects. This is essential in the evaluation of extended-release oxybutynin products to ensure that approved generics are therapeutically equivalent to the innovator product, and that no unexpected tolerability or safety concerns arise, especially in the elderly, once the product is in widespread use to treat the symptoms of overactive bladder.

B. OROS Oxybutynin Provides for Distinct Ratios of Parent and Metabolite Enantiomers Under Fasting and Fed Conditions

1. Presystemic Gut-Wall Metabolism of Oxybutynin Leads to Nonlinear Absorption Dependent on Release Rates and Gastrointestinal Transit Times

Oxybutynin is metabolized into the active desethyloxybutynin metabolite primarily by cytochrome P450 3A4 (CYP3A4) isoenzyme. It undergoes extensive and variable, presystemic, first-pass metabolism, resulting in a low mean oral bioavailability of about 6%.[49] The upper small intestine serves as the major site for intestinal CYP3A-mediated first-pass metabolism and may explain some of the interindividual differences in the oral bioavailability of some CYP3A substrates[50], including oxybutynin. The CYP3A content of

[47] Noronha-Blob L, Kachur JF. Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2, and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis, and salivary secretion in guinea pigs. *J Pharmacol Exp Ther* 1991;256:562-7.

[48] Smith ER, Wright SE, Aberg G. Comparison of Antimuscarinic and antispasmolytic actions of racemic oxybutynin and desethyloxybutynin and their entantiomers. *Arzneim Forsch Drug Res.* 1998, 48:1012-8.

[49] Douchamps J, Derenne F, Stockis A, *et al.* The pharmacokinetics of oxybutynin in man. *Eur J Clin Pharmacol* 1988;35:515-20.

[50] Paine MF, Khalighi M, Fisher JM, *et al.* Characterization of Intestinal and Intraintestinal Variations in Human CYP3A-Dependent Metabolism. *J Pharmacol Exp Ther* 1997, 283:1552-62.

both the liver and small intestine is highly variable among individuals, with > 11-fold variation found in human duodenal biopsies.[51]

In addition to low bioavailability of oxybutynin, values of maximum and total systemic exposure (CMAX and AUCINF) also exhibit high interindividual variability after oral administration. Although genetic polymorphism of CYP3A4 was suggested to cause such variability[52], this explanation is not consistent with the correlation of high oxybutynin with high desethyloxybutynin plasma concentrations. Instead, absorption differences among individuals most likely account for the wide range of systemic concentrations for the same molar dose.[53]

The absorption of oxybutynin is affected by differences in the pharmaceutical dosage form (eg, formulations and delivery technologies) and drug release rate, which are further compounded by individual differences in physiology of gastrointestinal tract and distribution of CYP3A4. Factors that affect gastrointestinal transit time of the dosage form, such as food, disease, or age, may alter the location where oxybutynin is mainly released and absorbed. Exposure of the dosage form to changes in physiological pH (acidic environment of the stomach versus neutral of the small intestine) and drugs that affect pH, such as antacids and proton pump inhibitors, have the potential to change release rates and site-specific absorption, depending on the type of drug delivery technology involved.

The OROS delivery system of DITROPAN XL is a nondisintegrating dosage form that reaches the colon in about three to five hours[54,55] after dosing under fasting conditions. Gamma scintigraphy was used to determine the transit time of an OROS delivery system containing oxprenolol after fasting.[56] Gastric emptying times were around one hour, and OROS units arrived in the colon in about four hours on average. Colonic transit time exhibited wide interindividual variability, ranging from six to 32 hours (median, 24.7 hours). Although oxybutynin is continuously released throughout the gastrointestinal tract over 24 hours, it is mainly released in the colon where there is less CYP3A4. Consequently, the

[51] Lown KS, Kolars JC, Thummel KE, *et al.* Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bladder *Drug Metab Dispos* 1994; 22:947-55.

[52] Ibid. 49.

[53] Hughes KM, Lang JCT, Lazare R, *et al.* Measurement of oxybutynin and its N-desethylmetabolite in plasma, and its application to pharmacokinetic studies in young, elderly, and frail elderly volunteers. *Xenobiotica* 1992; 22:859-69.

[54] Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms through the small intestine. *Gut* 1986, 27:886-92.

[55] Davis SS, Washington N, Parr GD, *et al.* Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal tract as determined by scintigraphy. *Br J Clin Pharmacol* 1988; 26:435-43.

[56] Ibid. 55.

metabolite-to-parent concentration ratios are markedly lower than those for immediate-release tablets, and they also differ from ratios reported for another extended-release oxybutynin product (CYSTRIN CR[57,58]) that employs a slowly swelling, erodible matrix tablet as the drug delivery technology.

For extended-release products containing oxybutynin, which undergoes site-specific metabolism in the upper small intestine, food effects on gastrointestinal time can change the metabolite-to-parent concentration ratios. Because food slows gastric emptying and can increase the gastrointestinal transit time of the contents, the potential exists for altering the residence time of and delivery rate from extended-release oxybutynin products. Nondisintegrating capsules, tablets, and osmotic pumps and slow-releasing tablets are retained in the stomach from one to nine hours with food, whereas small intestine transit remains around three hours,[59] similar to fasting conditions.

In a food-effect study[60] of CYSTRIN CR, men and women who ingested a 10-mg tablet two hours after a standard high-fat breakfast had statistically higher plasma concentrations of metabolite than when they ingested the controlled-release tablet under fasting conditions. The C_{MAX} of oxybutynin and desethyloxybutynin after food increased relative to fasting (4.3 versus 2.5 ng/ml, and 70.1 versus 43.2 ng/ml, respectively). The AUC of desethyloxybutynin also increased significantly with food (474 versus 391 ng·h/mL). These shifts to higher metabolite concentrations under fed conditions were also correlated with lower saliva secretion rates in the same study. The greatest decrease in saliva production was measured when subjects ingested the CYSTRIN CR tablet two hours after breakfast, which is consistent with the higher plasma concentrations of desethyloxybutynin.

By contrast, the OROS delivery technology of DITROPAN XL is not affected by food. In a standard food-effect bioavailability study,[61, 62] the 90% confidence intervals were well within the 80.0% to 125.0% range for the ratio of log-transformed AUC_{INF} means (fed/fasted) for the R- and S-enantiomers of both oxybutynin and desethyloxybutynin. They were also within the equivalence range for the ratio of log-transformed C_{MAX} means for R- and S-oxybutynin, but slightly wider for R- and S-desethyloxybutynin (119%-139% and 110%-

[57] At this time, CYSTRIN CR® (oxybutynin) Tablets are not approved by FDA for marketing in the United States, but they have been approved and marketed in Finland since 1998.

[58] Lukkari E, Aranko K, Juhakoski A, *et al.* Effect of time interval between food and drug ingestion on the absorption of oxybutynin from a controlled-release tablet. *Pharmacol Toxicol* 1997;81:31-4.

[59] Ibid. 54.

[60] Ibid. 58.

[61] NDA 20-897, ALZA Study C-96-074, 12/1997

[62] Sathyan G, Weiting H, Gupta SK. Lack of effect of food on the pharmacokinetics of an extended-release oxybutynin formulation. *J Clin Pharmacol* 2001, 41:187-92.

127%, respectively). The lack of a food effect on DITROPAN XL is reflected in its label[63] with the statement that the rate and extend of absorption and metabolism of oxybutynin are similar under fasting and fed conditions. Therefore, generic versions of DITROPAN XL, especially those that employ different drug delivery technologies, should have similar rates and extents of absorption and metabolism under fed conditions, as established by the bioequivalence of both oxybutynin and desethyloxybutynin.

This comparison of extended-release oxybutynin products clearly illustrates that the drug delivery technology employed to impart slower release and absorption over 24 hours can be an important contributor to the concentration ratios of active metabolite and parent, and that the contribution is magnified when the delivery technology, unlike OROS, is sensitive to administration with food. Because of complex interactions among drug delivery technology, food, gastrointestinal transit time, and site-specific metabolism, bioequivalence criteria should be applied to oxybutynin and its metabolite in the *food-effect* single-dose study of extended-release oxybutynin products in healthy volunteers.

2. *Pharmacologic Activity and Human Pharmacodynamics Differs Among Oxybutynin, Desethyloxybutynin, and Their Enantiomers*

Muscarinic receptors are widely distributed throughout the body, and have been classified into five subtypes (M_1 to M_5). The human detrusor muscle of the bladder contains a mixed population of M_2 and M_3 subtypes. Although the M_2 predominates at about 80%, bladder contraction is mediated by M_3 receptors.[64] Oxybutynin's anticholinergic activity, relative binding to antimuscarinic receptor subtypes (M_1, M_2, and M_3), and cystometric activity are stereoselective in animal tissues.[65,66] The R-oxybutynin enantiomer has been shown to exert higher anticholinergic activities than the racemic mixture and S-enantiomer[67] the latter of which contribute more to the spasmolytic effects of oxybutynin.[68]

Pharmacologic studies using human tissue from the detrusor muscle and salivary gland show that oxybutynin's metabolite, desethyloxybutynin, also acts as a competitive antagonist at muscarinic receptors.[69] Although oxybutynin and desethyloxybutynin have

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[63] Ibid. 19

[64] Wang P, Luthin Gr, Ruggieri MR. Muscarinic acetylcholine receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. *J Pharmacol Exp Ther* 1995;273:959-66.

[65] Kachur JF, Peterson JS, Carter JP. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther* 1988;247:867-72.

[66] Ibid. 47.

[67] Ibid. 47.

[68] Ibid. 48.

[69] Ibid. 45.

similar binding characteristics and *in vitro* antimuscarinic effects, the affinity to receptors in the salivary gland of the metabolite is significantly higher than that of the parent.[70] Because desethyloxybutynin exhibits antimuscarinic activity, the rate and extent of its formation will influence the time course and amplitude of both clinical and untoward anticholinergic effects, such as lowering saliva production, which leads to dry mouth.

3. Stereoselective Metabolism and Pharmacokinetics of Oxybutynin

Oxybutynin exhibits stereoselective metabolism and pharmacokinetics in which preferential oxidation of R-oxybutynin leads to its lower bioavailability compared with the S-enantiomer, and significantly higher systemic exposure to R-desethyloxybutynin. In a pharmacokinetics study[71] that evaluated a 5-mg immediate-release tablet, mean metabolite-to-parent ratios of the R-enantiomers for C_{MAX} and AUC_{INF} were about 8.9 and 21.5, respectively, whereas they were only 3.3 and 8.3, respectively, for the S-enantiomers. In the same study, an oxybutynin transdermal patch had metabolite-to-parent ratios of the R- and S-enantiomers for C_{MAX} and AUC_{INF} that ranged from only 0.8 to 1.0. These marked differences in the concentration ratios between the modes of administration (oral having very high ratios and transdermal having ratios near unity), and between the enantiomer ratios after oral administration, are highly consistent with oxybutynin's extensive presystemic gut-wall oxidation by CYP3A4 isoenzymes and with the stereoselective metabolism of the R-enantiomer.

For DITROPAN XL, bioavailabilities of the R- and S-enantiomers of parent and metabolite relative to those for an immediate–release tablet further illustrates the stereoselective metabolism of oxybutynin.[72] The relative bioavailability for R-oxybutynin is lower at 156% compared with 187% for the S-enantiomer, but both parent enantiomers are more bioavailable (>100%) when dosed using OROS extended-release tablets. The latter findings are consistent with bypassing some upper small intestinal metabolism to desethyloxybutynin. The relative bioavailabilities for R- and S-desethyloxybutynin were lower for DITROPAN XL at 73% and 92%. Changes in the relative bioavailabilities of each active moiety, primarily due to release rate differences between the immediate- and extended-release formulations and site-specific metabolism, lead to a different pattern of exposure for the parent drug and metabolite, and therefore, a different safety and efficacy profile.

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[70] Ibid. 45.

[71] Zobrist RH, Schmid B, Feick A, *et al.* Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharm Res* 2001;18:1029-34.

[72] NDA 20-897, ALZA Clinical Study Report C-96-074-02, 12/1997.

In terms of the distribution of isomers, they do not appear to be affected by post absorption mechanisms as the inversion of the S-enantiomer of both oxybutynin and desethyloxybutynin does not occur *in vivo*. In a pharmacokinetics study[73] in which only S-oxybutynin (5 to 320 mg) was dosed in healthy men and women, neither R-oxybutynin nor R-desethyloxybutynin were detected in plasma. No pharmacokinetics studies dosing only R-oxybutynin have been conducted, so it is unknown whether the R configuration of either the parent or metabolite inverts to the S configuration.

C. Primary Efficacy and Safety Activity Resides With the R-Enantiomers of Oxybutynin and its Metabolite, and Thus, With their Relative Concentrations

R-oxybutynin is the minor enantiomer as defined by total and maximum systemic exposure (AUC_{INF} and C_{MAX}) relative to that of the S-enantiomer, whereas R-desethyloxybutynin is the major enantiomer of the active metabolite pair. For oral pharmaceutical dosage forms, stereoselective metabolism of racemic oxybutynin decreases the bioavailability of R-oxybutynin such that its concentrations are lower and R-desethyloxybutynin higher than those for the S-enantiomers. Moreover, the release profile and delivery technologies can further alter the relative concentrations of metabolite to parent for both enantiomers due to site-specific metabolism in the gastrointestinal tract. This would be important to consider when evaluating different extended-release oxybutynin products in the treatment of overactive bladder, because R-oxybutynin compared with S-oxybutynin is primarily responsible for the anticholinergic effects that contribute to clinical efficacy and safety, and R-desethyloxybutynin compared with R-oxybutynin is primarily responsible for the untoward anticholinergic effects that contribute to tolerability and safety.

Data that support the major role of R-oxybutynin are provided in a study assessing *in vivo* activity,[74] in which R-oxybutynin was shown to be 21- to >100-fold more potent than S-oxybutynin at inhibiting bladder volume-induced contractions, 136-fold more potent at inducing mydriasis, and 30-fold more potent at inhibiting salivation. R-oxybutynin was also reported to be more potent than S-oxybutynin in another study utilizing several *in vitro* and *in vivo* assays related to the safety and efficacy of oxybutynin.[75] Thus, although plasma concentrations of R-oxybutynin are lower than S-oxybutynin after oral administration of

[73] Koch P, McCullough, Blum PS, *et al.* Pharmacokinetics and safety of (s)-oxybutynin in normal healthy volunteers. [abstract # 825] *FASEB* 1998;12:A142.
[74] Ibid, 47.
[75] Ibid. 65.

racemic drug formulations,[76] this minor enantiomer contributes greater pharmacologic activity.

Clinical study data support the major role of R-desethyloxybutynin in contributing to the tolerability and safety of oxybutynin. The concentration-effect relationship between each R-enantiomer and dry mouth was evaluated in a double-blind, pharmacokinetics-pharmacodynamics study[77] comparing four days of dosing with DITROPAN XL 10mg in the morning and immediate-release oxybutynin 5 mg in the morning and eight hours later. The decrease in salivary output and consequent increase in dry mouth severity on a 100 mm visual analogue scale were correlated with plasma R-desethyloxybutynin concentrations, but no relationship with R-oxybutynin concentrations was observed. These results further support that the untoward anticholinergic effects associated with oxybutynin's tolerability and safety resides primarily with R-desethyloxybutynin concentrations.

As stated previously, the stereoselective metabolism and absorption of oxybutynin is affected by differences in the pharmaceutical dosage form (eg, formulations and delivery technologies) and drug release rate, which are further compounded by individual differences in physiology of the gastrointestinal tract and distribution of CYP3A4 isoenzymes. Factors that affect gastrointestinal transit time of the dosage form, such as food, disease, or age, may also alter the location where oxybutynin is mainly released, metabolized, and absorbed. Data from seven published or company-sponsored pharmacokinetic studies are summarized in Table 1, in which differences in metabolite-to-parent concentration ratios among oxybutynin products with different modes of administration, formulations, and release rates are shown.

Total systemic exposure (AUC_{INF}) for desethyloxybutynin is about 10-fold higher than oxybutynin for both the immediate-release tablet and a once-daily, extended-release tablet that utilizes a swelling, erodible matrix. In contrast, desethyloxybutynin concentrations are only about 5-fold higher than oxybutynin for DITROPAN XL, and they are about equal for the transdermal patch, the latter of which totally bypasses first-pass metabolism in the gut. When the metabolite-to-parent ratios for the most potent R-enantiomers are compared, differences among the oral products are magnified: desethyloxybutynin systemic exposures are about 20- and 10-fold higher for the immediate-release tablet and DITROPN XL, respectively.

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[76] Ibid. 62.
[77] Ibid. 26.

The clinical relevance of these pharmacokinetic differences among oxybutynin products is demonstrated by the consistency in reports of adverse anticholinergic effects across several published and company-sponsored clinical trials. The adverse event data for dry mouth are summarized as head-to-head treatment comparisons within a study or set of studies in Table 2. Desethyloxybutynin is responsible for other adverse antimuscarinic effects, but dry mouth was selected to illustrate the relationship between exposure and safety. It is reported in all clinical studies, and can also be readily quantified in pharmacodynamic studies using the decrease in saliva production as a surrogate.

In Table 1, the higher metabolite-to-parent concentration ratio for immediate-release tablets compared with both DITROPAN XL extended-release tablets and the OXYTROL patch is consistent with the higher percentages of patients reporting dry mouth, including moderate-to-severe reports (Table 2). In addition, the lower metabolite concentrations for the patch compared with DITROPAN XL are associated with the lowest dry mouth reports, which are about equal to placebo. In contrast, the CYSTRIN CR extended-release tablet had a metabolite-to-parent concentration ratio comparable to the immediate-release tablet, and also had similar reports of dry mouth in the clinical studies. Although the pharmacokinetics and clinical safety data are derived from different studies comparing oxybutynin products, the pattern of high metabolite ratio associated with high reports of adverse anticholinergic effects is evident. Because of the important role desethyloxybutynin has in the balance of tolerability and efficacy, it should be evaluated along with oxybutynin in bioequivalence studies.

Table 1. Effect of Administration Mode and Drug Release Rate on Racemic and Enantiomer Metabo

Oxybutynin Dosage Form	Product Name	Daily Dose	Subjects Male / Female	Metabolite-to-Parent AUCINF Ratio Tot-DES/OXY	R-DES/OXY	S-DES/O
Immediate-Release	DITROPAN	3 X 5 mg	21M / 20F	11 [a]	18 [a]	6 [a]
Disintegrating Tablet	DITROPAN	1 X 5 mg	8M / 10F	11 [a]	22 [b]	8 [b]
	CYSTRIN	1 X 5 mg	17 F	12 [a]	unk	unk
Extended-Release	DITROPAN XL	1 X 15 mg	21M / 29F	5 [b]	8 [b]	3 [b]
OROS Osmotic Tablet		1 X 10mg	21M / 20F	5 [a]	9 [a]	3 [a]
Extended-Release	CYSTRIN CR	1 X 10mg	11M / 12F	12 [a]	unk	unk
Erodible Matrix Tablet		1 X 10mg	15M / 14F	13 [a]	unk	unk
		1 X 10mg	16F	8 [a]	unk	unk
		1 X 10mg	25M	12 [b]	unk	unk
		1 X 10mg	24F	13 [b]	unk	unk
Transdermal Matrix-Type Patch	OXYTROL	36 mg 96 h	8M / 10F	0.9 [a]	1.0 [b]	0.8 [b]

Key: OXY – oxybutynin, DES – desethyloxybutynin, Tot – total, unk – unknown

a: Metabolite-to-parent ratio estimated from reported mean values of AUCINF for each moiety. b: Ratio reported in publication or individual ratios.

[78] NDA 20-89, ALZA Clinical Study Report C-96-074-02, 12/1997

[79] Ibid. 71.

[80] Ibid. 36.

[81] ALZA Clinical Study Report C-98-014, Data on File.

[82] Lukkari E, Castren-Kortekangas P, Juhakoski A, *et al.* Effects of food on the bioavailability of oxybutynin from a controlled *Pharmacol* 1996;50:221-3.

[83] Ibid 58.

[84] Lukkari E, Hakonen T, Neuvonen PJ. The pharmacokinetics of oxybutynin is unaffected by gender and contraceptive steroi 1998; 53:351-4.

Table 2. Head-to-Head Clinical Comparisons of Anticholinergic Adverse Effects Among Oxybutynin Product

	Daily Dose Range	N	Dry Mouth (%) Mild	Moderate	Severe	Total	
DITROPAN XL Tablet vs	5 to 30 mg	344	53.1 [a]	24.5 [a]	4.1 [a]	61.8	NDA 2(
Immediate-Release Tablet	5 to 20 mg	84	82.1 [a]	44.0 [a]	9.5 [a]	89.3	
CYSTRIN CR Tablet vs	10 mg	79	--	--	--	27.8	Birns 2(
Immediate-Release Tablet	10 mg	84	--	--	--	33.3	
OXYTROL Patch vs	2.6 to 5.2 mg	38	27	11	0	39	Davila 2
Immediate-Release Tablet	10 to 22.5 mg	38	26	59	9	82	
OXYTROL Patch vs	3.9 mg	246	--	--	--	6.9	OXYTR
Placebo	N/A	249	--	--	--	5.2	Februa

[a] Values presented for mild, moderate, and severe dry mouth include reports deemed to be treatment-related.

[b] All subjects received two weeks of immediate-release oxybutynin in a screening phase before randomization to either treatmen due to adverse events in this screening phase, which may have lowered the final rates of dry mouth reported in the treatment ph and immediate-release products.

[85] Ibid 35.

[86] Ibid 36.

[87] Davila GW, Daughtery CA, Sanders SW, *et al.* a short term, multicenter, randomized double-blind dose titration study of the e side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J U*

D. Differences in the Relative Systemic Concentrations of Metabolite and Parent Among Oxybutynin Products Can Impact Patient Treatment Outcomes

DITROPAN XL has six approved doses (5, 10, 15, 20, 25, and 30 mg) available for titration. The recommended starting dose is 5 or 10 mg once daily, and doses may be adjusted in 5-mg increments at weekly intervals up to a maximum of 30 mg[88] to achieve the optimal balance of efficacy and tolerability for each patient. Doses can be adjusted downwards if intolerable anticholinergic effects emerge, such as dry month, blurred vision, dizziness, and constipation.

The ability to individualize oral doses of oxybutynin requires that the drug product have an adequate therapeutic index that allows efficacy to be achieved without emergence of intolerable adverse effects. This is particularly necessary for elderly patients who may be sensitive to central nervous system actions of anticholinergic drugs, and for patients taking proton pump inhibitors that alter gastrointestinal pH. Until the availability of DITROPAN XL, an extended-release oxybutynin product, and a transdermal patch, in which the metabolite-to-parent concentration ratios have decreased compared with the original immediate-release products, the intolerable effects of oxybutynin would sometimes limit the ability to attain satisfactory treatment outcomes. In these cases, the titrated dose was often minimally effective in order to improve patient comfort and adherence to treatment.

Therapeutic indices for DITROPAN XL and the immediate-release tablet over a range of doses were approximated from modeling clinical and safety data[89] from two double-blind studies. The relationships between dose and urge urinary incontinence and between dose and dry mouth were combined in this model, and they predicted a wider therapeutic index for DITROPAN XL. This prediction is consistent with the stereoselective metabolism and pharmacokinetics data presented previously in that DITROPAN XL has lower systemic concentrations of R-desethyloxybutynin. The wider therapeutic index supports titrating to higher effective doses.

Data from a double-blind, dose-titration clinical study[90] comparing DITROPAN XL and immediate-release tablets illustrate the effect of relative differences in the metabolite and parent systemic exposures. A higher proportion of subjects undergoing dose titration with DITROPAN XL were able to reach their final doses of 15 or 20 mg/d compared with patients taking immediate-release oxybutynin tablets (38.7% versus 31.3%, respectively). In addition, a dose-related increase in the incidence of dry mouth was noted for each

[88] Ibid. 19.
[89] Ibid. 33.
[90] NDA 20-89, ALZA Clinical Study Report C-97-020, 12/1997.

treatment. Although differences in the overall incidence of dry mouth between groups, which included treatment across all doses, failed to reach statistical significance (47.7% for DITROPAN XL versus 59.1% for immediate-release oxybutynin; p = 0.09), a Kaplan-Meier analysis of first report to dry mouth at each dose revealed that a significantly lower proportion of DITROPAN XL subjects had moderate-to-severe dry mouth (p = 0.007) or any dry mouth (p = 0.003).

V. CONCLUSIONS

- The active metabolite of oxybutynin, desethyloxybutynin, is formed by presystemic gut-wall metabolism, and contributes meaningfully to the safety and efficacy of oxybutynin. Stereoselective metabolism and pharmacologic activities also have important roles in the overall safety and efficacy of oxybutynin products, as the rates of drug release determine the relative formation of R and S enantiomers of metabolite and parent. The OROS drug delivery technology of DITROPAN XL, with its specific release-rate profile and insensitivity to food, contributes uniquely to the resulting metabolite-to-parent concentration ratios and pattern of system exposures.
- Clinical study data demonstrate that differences among oxybutynin products in the expression and tolerability of untoward anticholinergic effects and adherence to treatment by patients can be attributed to relative differences in the metabolite and parent concentrations. For extended-release oxybutynin products, bioequivalence decisions based solely on oxybutynin plasma concentrations are insufficient without consideration of desethyloxybutynin and the inherent stereoselective differences of both active moieties. This can lead to the inappropriate approval of generic products deemed bioequivalent, which ultimately prove to have very different adverse effect and safety profiles once in widespread use for overactive bladder.
- ALZA Corporation developed DITROPAN XL and recognized the importance of delineating the pattern of systemic exposures for the R and S-enantiomers of oxybutynin and desethyloxybutynin as they relate to the safety and efficacy profile. Consistent with this standard, bioequivalence of the clinical and commercial OROS formulations was established by applying FDA's bioequivalence metrics and confidence interval criteria *a priori* to the R- and S-enantiomers of both oxybutynin and desethyloxybutynin.[91]

[91] NDA 20-897, ALZA Clinical Study Report C-97-015-01, 12/1997.

Therefore, Ortho Urology requests that FDA require bioequivalence criteria be applied separately to both oxybutynin and desethyloxybutynin, rather than only measure the active metabolite, to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin products. Moreover, application to the two active moieties of oxybutynin should be required in bioequivalence studies conducted under both fasting and fed conditions.

C. ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Ortho Urology will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Very truly yours,
ORTHO UROLOGY

Minnie Baylor-Henry

Minnie Baylor-Henry
Vice-President, Medical and Regulatory Affairs