NDA 20-897 **SE8**-009
NDA 17-577 **SE8**-033
NDA 18-211 **SE8**-016

BPCA Clinical Summary Review

Drugs: Ditropan XL extended release tablets (oxybutynin chloride)
Ditropan Tablets (oxybutynin chloride)
Ditropan Syrup (oxybutynin chloride)

On the basis of the clinical and clinical pharmacology reviews, these three pediatric efficacy supplements may be **approved**. The sponsor has provided substantial new clinical efficacy and safety information to support a new pediatric indication for Ditropan XL. Additional clinical and clinical pharmacology information in children has been submitted to support new labeling in the corresponding sections of the Ditropan Tablets and Syrup label, two products already approved for use in children.

Two studies were conducted. The first (**C-2000-042-01**) was a large efficacy, safety and pharmacokinetic evaluation in approximately 116 children with detrusor overactivity related to neurogenic conditions (e.g. spina bifida). This was 24 weeks in duration, included all three Ditropan formulations and assessed efficacy using both clinical parameters (via voiding diary and catheterization schedules) and urodynamic parameters (maximum bladder capacity, detrusor pressures at maximum capacity, and volume at first involuntary detrusor contraction). In addition, sparse sampling for serum oxybuynin chloride concentrations was used to derive pharmacokinetic parameters for each formulation. Finally, safety was assessed by clinical adverse events, serum laboratories and EKGs. The second study (**C-2000-043-01**) was a smaller pilot (or exploratory) study of Ditropan Syrup in children less than aged six with known myelomeningocele. The rationale in this case was that "prophylactic" anticholinergic treatment might improve long-term bladder function in these children. This type of treatment had been reported in the clinical literature and was being used by some practicing pediatric urologists. Therefore, the study was a short (13 to 28 days) and small study (n=16). The efficacy parameters were from urodynamic studies (especially focusing on bladder pressures).

For **Study 042**, the mean duration of exposure to oxybutynin was 24.3 weeks (range 6 to 31 weeks). Sixty-one patients received Ditropan XL, 30 received Ditropan Syrup and 28 received Ditropan Tablets. (These numbers tally >116 because 3 patients switched formulation during the trial.) The doses taken during the trial for Ditropan XL were either 10 or 15 mg once daily. The total daily doses taken for Syrup were 5mg to 30mg, and for Tablets 5mg to 15mg, both in BID, TID or QID divided doses. The total daily oxybutynin dose on a mg/kg basis was either 0.20-<40 mg/kg (46%), or 0.40-<0.60mg/kg (34%) in the majority of patients. Clinical efficacy results demonstrated the benefit of oxybutynin on urine storage. Improvements were noted in the "all enrolled" group (N=116) in terms of increasing average urine volume per catheterization, increasing urine volume after morning awakening, and increasing percentage of catheterizations without a leaking accident. The exact figures for these endpoints may be found in Dr. Gierhart's March 21, 2003 review in Tables #2, #3 and #4. A summary of this data was translated to the appropriate product labels as follows:

At total daily doses ranging from 5 mg to 15 mg, treatment with **Ditropan Tablets** was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%.

At total daily doses ranging from 5 mg to 30 mg, treatment with **Ditropan Syrup** was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%.

Administration of **DITROPAN XL** 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results measured over time were consistent with these clinical results. These included: increases in maximum cystometric bladder capacity, decreases in detrusor pressure at maximal bladder capacity (a particularly welcome finding), and an increases in the percentage of patients with no inhibited detrusor contractions. These results were translated to the labels as follows:

Treatment with **Ditropan Tablets** was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

Treatment with **Ditropan Syrup** was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H_20 to 37 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 67% to 28%.

Administration of **DITROPAN XL** resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

Forty-two (42) patients out of the total 116 “all enrolled group” underwent sparse sampling for oxybutynin chloride serum concentrations. In this group, 19 were taking Ditropan XL, 11 were taking Ditropan Tablets, and 12 were taking Ditropan Syrup. The total daily dose was 10mg in 43% of these patients and 15mg in 41%. The total daily dose on a mg/kg basis was 0.20-<0.40 mg/kg in 50% and 0.40-<60mg/kg in 31% of these patients. Twenty-five children in the pK subgroup were <=10 years of age and 17 were older than 10 years. The medical officer was unable to determine any relationship between total daily dose or total daily dose in mg/kg and pharmacokinetic parameters. However, our clinical pharmacology were successful in using all the available data to derive some pK conclusions. Specifically, for Ditropan Tablets and Syrup,

when all available data were normalized to a total dose of 5 mg BID or TID, the pK parameters at steady state were translated to the label as Tables #1 and #2 and Figure #1 that follow:

Table 1. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State (N=11).

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

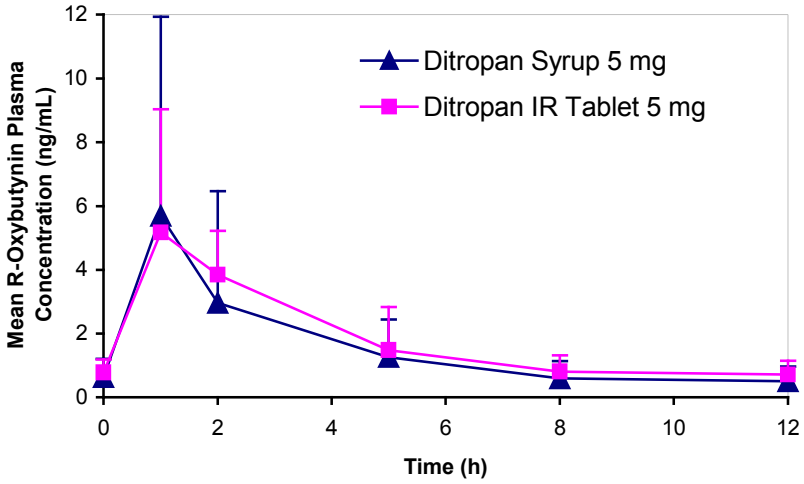
*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Table 2. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State (N=12).

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max*} (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Figure 1. *Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

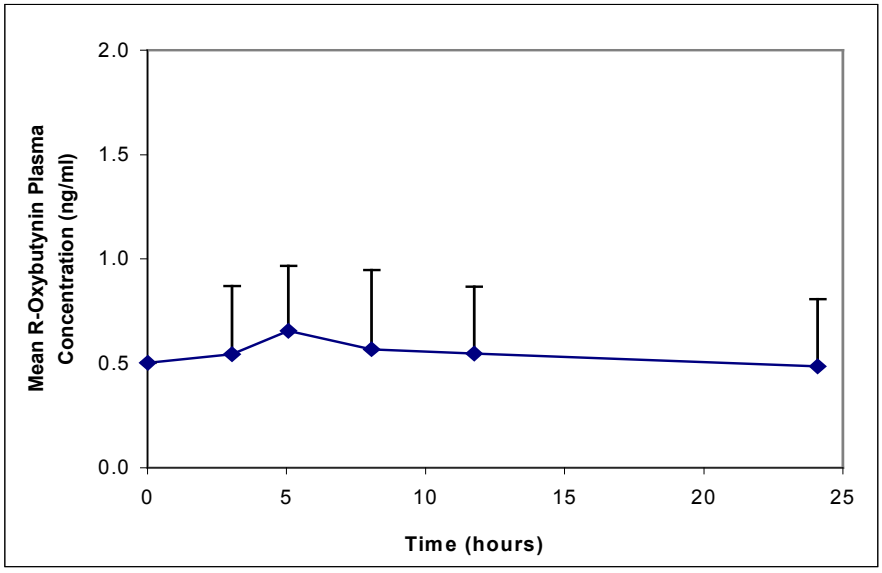


For Ditropan XL, the label reflects the following derived pharmacokinetic parameters in children:

Table 3. Mean R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily. All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily. (N=19)

	R-Oxybutynin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.2 ± 0.8	6.8 ± 3.5	3.8 ± 2.2
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*



For additional information relevant to this pharmacokinetic information, the reader is referred to Dr. Chatterjee's detailed review of these supplements.

In terms of safety, there were no unexpected adverse events and no worrisome findings in terms of frequency or severity of adverse event reports.

For **Study 043**, a total of 16 patients were enrolled at 3 sites in the US and one site in the Netherlands. Ten of these children were enrolled at the Netherlands site. The median age was 3 years and range from 1 to 5 years. Five of the children were 2 years old. The majority of patients were male (69%) and Caucasian (75%). Median weight was 16 kg and ranged from 11 kg to 20 kg. Patients were all known to have detrusor hyperreflexia as a consequence of neurological conditions and were already on a stable dose of oxybutynin. Seventy percent reported a concurrent fecal impaction condition. Efficacy was assessed by urodynamic studies at baseline and after at least two weeks on treatment. The urodynamic parameters of interest were maximal cystometric capacity, intravesical pressure, and presence of uninhibited contractions. The purpose of these measurements was to assess whether oxybutynin treatment improved capacity while lowering or maintaining intravesical pressure.

Maximal capacity increased from baseline by a mean of 71.5 mL with a range of improvement from 29 mL to 265 mL. On the other hand, mean detrusor pressure at maximal capacity increased slightly, as reflected by a mean increase of 0.6 cm H_20 (range from –21 cm H_20 to +50 cm H_20). There was a reduction in the percentage of patients demonstrating involuntary detrusor contractions (IDCs) of at least 15 cm H_20 from 11 of 16 patients (69%) to 2 of 16 patients (12.5%). Thus, treatment of these children was associated with improvements in maximal vesical capacity and reduction in the percentage of patients demonstrating IDCs, but the most important factor, change-from-baseline in mean detrusor pressure, actually increased slightly. In fact, in some children, the detrusor pressures went up markedly (+50 cm H_20). In ten of the 16 children, detrusor pressures at baseline were fairly low (< 40 cm H_20).

Until additional research supports clinical benefit of this mode of treatment or until a specific subgroup of children are defined in whom this treatment is effective without increasing bladder pressures (increasing capacity and decreasing or maintaining pressures), these results appear to preclude approval of this novel indication. This should not be construed by the reader to mean that this type of treatment may not one day be shown effective in at least some patients.

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Daniel A. Shames

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