



NDA 7-959/S-013/S-015

ICN Pharmaceuticals, Inc.  
Attention: Edward F. Smith III, Ph.D.  
Director, Corporate Regulatory Affairs  
ICN Plaza – 3300 Hyland Ave.  
Costa Mesa, CA 92626

Dear Dr. Smith:

Please refer to your supplemental new drug applications dated January 24, 1994 (NDA 7-959/S-013), and October 22, 1998 (NDA 7-959/S-015), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tensilon (edrophonium chloride) 10 mg/ml Injection.

Supplemental application, S-013, submitted under “Changes Being Effected” provides for the following changes:

1. The removal of pralidoxime chloride as a treatment for edrophonium chloride overdose in the **OVERDOSAGE** section of labeling as requested in an Agency letter dated September 2, 1993.
2. The removal of the terms “or inactivation” to reflect that edrophonium chloride is a competitive inhibitor rather than an irreversible inhibitor of acetylcholinesterase under the **ACTIONS** section of labeling.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted on January 24, 1994. Accordingly, this supplemental application is approved effective on the date of this letter.

Supplemental application, S-015, submitted as a “Prior Approval” supplemental new drug application provides for the following labeling revisions:

The addition of two new subsections entitled **ACTIONS-Pediatric Pharmacology** and **PRECAUTIONS-Pediatric Use**. It also changes, in the **DOSAGE AND ADMINISTRATION** section, at each occurrence, “children” to “pediatric patients”. We note that this additional pediatric information was submitted in order to comply with a December 13, 1994 Federal Register Notice.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised labeling as follows (double underline font denotes our additions to the labeling proposed in your October 22, 1998 submission):

**Under ACTIONS-Pediatric Pharmacology**

The pharmacology of Tensilon was studied in 14 infants (between 3 weeks and 11 months old) and 12 children (between 1 year and 6 years old) during a steady-state infusion of d-tubocurarine during N<sub>2</sub>O-halothane anesthesia and controlled ventilation for elective surgery. The ED<sub>50</sub> dose (dose producing 50% antagonism of 90% neuromuscular depression) for Tensilon was 145 ug/kg in infants and 233 ug/kg in children not significantly different from that observed in adult patients; however, there was greater variability among infants and children than adults. Time to peak antagonism and duration of antagonism were similar between the two pediatric age groups and adult patients. Tensilon pharmacokinetics were studied in four infants (3 months through 7 months of age) and four children (1 through 4 years of age). Total clearance was 17.8 mL/kg.min in infants and 14.2 mL/kg.min in children. Total clearance was significantly greater in infants than in adults (8.3 +-2.9 mL/kg.min) p<0.05. Elimination half-life was 73+-30 minutes in infants and 99 +-31 minutes in children compared with 126 +-59 minutes in adult patients. Volume of distribution in infants and children was 1.18 +-0.20 L/kg and 1.22 +-0.74 L/kg, respectively, compared with 0.90 +- 0.13 L/kg in adults.

**Under PRECAUTIONS-Pediatric Use**

The safety and effectiveness of Tensilon in the differential diagnosis of myasthenia gravis have been established in pediatric patients. (See DOSAGE AND ADMINISTRATION: Tensilon Test in the Differential Diagnosis of Myasthenia Gravis: Dosage in Pediatric Patients). The safety and effectiveness of Tensilon in reversing neuromuscular blockade in pediatric patients have not been fully determined, although doses ranging from 0.1 mg/kg to 1.43 mg/kg have been described. Antagonism of nondepolarizing neuromuscular blocking drugs in pediatric patients is more rapid than in adults. Limited pharmacodynamic and pharmacokinetic data in pediatric patients have been published. (See ACTIONS: Pediatric Pharmacology.)

The remainder of your revisions are acceptable.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Russell Katz

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