CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-595

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW

NDA 21- 595 SANCTURA (Trospium Chloride)

Application Information	
NDA #	**21-595**
Primary Efficacy Studies:	**IP631-003, IP631-005, MP94D2.14, MP94D2.15**
Submission Date:	**February 28, 2004**
PDUFA Goal Date:	**May 28, 2004**
Review Status:	**Standard**
Drug Name	
Generic Name	**Trospium chloride**
Proposed Trade Name	**Sanctura**
Drug Categorization	
Chemical Classification	**New Molecular Entity (NME)**
Pharmacological Class	**Anticholinergic**
Proposed Indication	**Treatment of Overactive Bladder**
Proposed Dose Regimen	**20mg BID**
Strength and Dosage Form	**20mg tablets**
Route of Administration	**Oral**
Reviewer Information	
Clinical Reviewer	**Suresh Kaul, MD, MPH**
Medical Team Leader	**Mark Hirsch, MD**
Division Director	**Dan Shames, MD**

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I. Executive Summary

1. Recommendations

In the opinion of this reviewer, from a clinical perspective, Trospium chloride 20-mg tablet taken twice daily **should be approved** for the indication of "**treatment of overactive bladder (OAB) symptoms** urinary urge incontinence

The evidence presented in the submission of this NDA is adequate in support of the effectiveness of trospium chloride. The adverse events profile of trospium chloride appears to be similar to other approved anticholinergic drugs in its class. The safety evaluation meets the ICH guidance for the number of subjects exposed to trospium and for the duration of exposure. QT safety assessment from study IP631-010 showed no signal of an effect at the clinical dose of 20-mg and up to 100-mg twice daily on cardiac repolarization or conduction. The QT study demonstrated evidence of tachycardia at supraphysiological blood concentrations and some t-wave inversions were seen in clinically asymptomatic patients.

2. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Trospium chloride is a quaternary ammonium derivative of tropine with anticholinergic properties and peripheral muscarinic like activity, proposed for the treatment of symptoms of OAB. Trospium chloride antagonizes the effect of acetylecholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing smooth muscle tone, that enables the detrusor muscle to relax, thus inhibiting evacuation of the bladder.

Trospium chloride is absorbed following an oral ingestion with maximum plasma concentration seen in approximately 5 hours post dose. The mean absolute bioavailability is approximately 10%. Administration with high fat meal results in reduced absorption, with AUC and Cmax values 70-80% lower than those obtained when trospium is administered fasting.

During the a pre-NDA meeting held on December 9 2002, it was agreed that one pivotal study (IP631-003) and a 9-month open-label extension conducted in the US would be acceptable, along with other short and long-term controlled studies conducted previously outside the U.S. During the same meeting, the Division also requested that the urge incontinence results be displayed in terms of change-per-week in addition to change-per-day (i.e., 24 hours) in order to capture the clinical relevance of trospium effect on incontinence experienced by patients with overactive bladder (OAB).

As of February 2004, the sponsor has completed 32 clinical trials involving over 2700 patients and subjects over a period of at least 3 weeks. A total of 500 patients were exposed to trospium chloride for at least 6 months, 315 of whom have been exposed to the study drug for at least one year.

In support of this **NDA 21-595**, the sponsor submitted data for two pivotal trials **(IP631-003 and IP631-005)** conducted in the United States along with several other active and placebo-controlled studies. The reviewer chose to focus primarily on the pivotal U.S. trials, the sponsor's Integrated Summary of Safety, and two other trials from Europe **(MP94D2.14** and **MP94D2.15)** as part of the overall review of efficacy and safety of trospium chloride for treatment of patients with overactive bladder. The design of all four studies was similar, with the two pivotals being nearly identical. The first pivotal study was conducted for 12 weeks with a 9-month open-label extension. The second pivotal study IP631-005 was also conducted for 12 weeks. The two additional supporting studies that the medical officer reviewed had treatment periods of 3-4 weeks each. A total of 1623 patients were randomized to receive either trospium or placebo in all four studies (trospium 877 and placebo 768).

B. Efficacy

The primary endpoints for the pivotal studies and the surrogate endpoints included in the supporting studies were appropriate and clinically meaningful. The study results provide substantial evidence in support of effectiveness of trospium chloride (20mg bid orally) for the treatment of patients 18 years and older with symptoms of overactive bladder (OAB).

The efficacy conclusions in all four studies were as follows:

- Trospium showed an improvement in toilet voids (urinary frequency) over a treatment period of 3 to 12 weeks in all four trials. Statistical significance was achieved in both pivotal trials at the $p<0.001$ level. The treatment effect was observed as early as Week 1. For study MP94D2.14, there was improvement with a statistical significance at the $p< 0.03$ level. For the supporting study MP94D2.15 the improvement in toilet voids was statistically marginal.
- For incontinence episodes, there were decreases shown in both pivotal studies and the improvements were statistically significant when compared to placebo. For the supporting studies the improvements were marginal.
- For volume voided, trospium increased the average volume per void. The increase was statistically significant at the $p <0.001$ level for both pivotal studies. There was also an improvement seen in urinary volume void in both supporting studies.
- Trospium demonstrated a decrease in the sensation of urgency (using a 4-point urgency severity scale) with a statistical significance at the $p<0.001$ level in both pivotal studies.
- Trospium also demonstrated a significant improvement in other clinically relevant secondary endpoints in all four studies reviewed.

- The magnitude of treatment effect was consistent across different age groups, race and gender.

C. Safety

In this medical officer's review, safety data is primarily drawn from a total of 1623 patients enrolled in four completed studies (2 conducted in the US and 2 conducted in Europe). The safety evaluation in general is adequate. The QT safety assessment from a previously submitted study (IP631-001) was inconclusive due to the lack of positive control, use of small sample size for randomization, and being an underpowered study. Subsequently, results from a larger, moxifloxacin-controlled study, IP631-010, were submitted to assess the effect of trospium chloride on the QT interval. These demonstrated no signal of any effect of trospium chloride on the QT interval at the clinical dose of 20mg twice daily or at a supra-therapeutic dose up to 100mg twice daily. However, there was evidence of t-wave inversion seen in several asymptomatic patients that is not believed to reflect a clinically meaningful diagnosis. There was also moderate tachycardia noted at the supraphysiological dose. In view of the findings from this study, this reviewer does not find any realistic risk of QT prolongation with the use of trospium chloride in patients with OAB.

The reported significant adverse events are primarily those related to known side effects of other approved anticholinergic drugs. No significant cardiovascular, hepatic, hematologic or renal toxicities were identified.

Important safety-related findings were:

- Dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation were the most frequently reported adverse events that occurred in the two pivotal studies.
- Majority of the reported clinical adverse events were mild to moderate in severity and resolved without any serious intervention.
- There was also a trend of increased anticholinergic adverse events (i.e., dry mouth, constipation, dyspepsia and urinary retention) seen in those patients 65 years and older in both the pivotal trials. This difference was more pronounced in those patients 75 years and older.
- The review of serious adverse events in the pivotal studies also focused on episodes of chest pain and other cardiovascular adverse events. There were a total of nine patients in the trospium group who experienced chest pain. None of these events, from either pivotal study, was determined to be due to myocardial ischemia.
- There were two patients who experienced angina in one of the pivotal trials. Both these patients had past medical history of angina, coronary artery disease, and other co-morbid medical conditions. None of these patients required any extraordinary medical intervention. These events were judged by the investigator as not being related to treatment with trospium chloride.
- There were three patients who experienced myocardial infarction. Two of the three patients had extensive previous co-morbid cardiac conditions and both recovered

from their events following intervention. These events were determined by the investigator to be not related to trospium chloride. The third patient, who was hospitalized for bowel obstruction, later developed myocardial infarction while being hospitalized. The relationship to trospium in this case was judged to be possible.

- There were two cases of vertigo reported in earlier Phase 1 human clinical pharmacology studies. Both these cases were determined to be unlikely related to trospium chloride and neither of them required any significant medical intervention.
- In the pivotal trials, there were two serious adverse events that resulted in death. In the first case, the patient was an 81-year-old male who suffered from a hemorrhagic stroke 57 days after the initiation of study drug. This patient was enrolled in the pivotal study IP631-003 and the cause of death was determined as not being related to the study medication by the investigator. The stroke was attributed to pre-existing amyloid angiopathy and hypertensive hemorrhage.

  In the second case, the patient was a 73-year-old male who developed bowel obstruction 21 days after the first dose of trospium chloride and later experienced myocardial infarction, which resulted in death. This patient was enrolled in study IP631-005. In this case, the investigator judged that a cascade of events ranging from previous abdominal surgery, presence of extensive abdominal adhesions and bowel obstruction to development of myocardial infarction could possibly be related to trospium chloride.

D. Dosing

The 20mg dose of trospium was selected based on results from Phase 1 and Phase 2 studies. Trospium chloride given at a dose of 20mg twice daily, was determined to be the maximally effective dose by sponsor in improving the symptoms of overactive bladder (OAB). To ensure efficacy, trospium should be given one hour prior to meals to avoid the reduced exposure that accompanies a high fat meal.

D. Special Populations

Effect on age, gender and race: Trospium chloride did not demonstrate any difference in effectiveness based on gender or race. However, there is an increase in the incidences of anticholinergic adverse events seen in those patients aged 65 years and older, and that was more pronounced in patients aged 75 years and older.

Elderly: There is evidence of an increased incidence of anticholinergic adverse events (i.e., dry mouth, constipation, dyspepsia and urinary retention) seen in patients 65 years of age and older, which is more pronounced in those 75 years of age and older. Sponsor believes that this is related to a heightened sensitivity to anticholinergic effects in the elderly and not due to any increase in systemic exposure. However, it still remains possible that these effects are related to increases in exposure secondary to decreased active renal secretory function in the elderly.

Renal impairment: Active renal secretion is an important elimination pathway for trospium. Studies assessing the effect of renal insufficiency on trospium pharmacokinetics indicate that a dose reduction in severe renal insufficiency is appropriate. Therefore, at the recommendation of the clinical pharmacology review team, sponsor has agreed to reduce the dose of trospium chloride in patients with creatinine clearance of <30ml/minute to 20mg once daily administered in the evening.

Hepatic impairment: Trospium chloride itself was not associated with any hepatic toxicity. In those patients with moderate hepatic impairment, maximum concentrations were only slightly increased, not requiring a dose adjustment. No studies were done in severe hepatic impairment. Therefore, a precaution in the label for patients with severe hepatic impairment (Child-Pugh C) on trospium chloride has been established.

Pediatric issues: Sponsor has been granted a partial waiver for conducting pediatric studies in children – years of age and younger, and a deferral of studies for children aged – to 15 years.

Use in Pregnancy Information: There are no adequate and well-controlled studies in pregnant women. As a pregnancy Category C drug, Sanctura should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. Similarly, trospium chloride was excreted to a limited extent into the milk of lactating rats. Therefore, Sanctura should only be used during lactation if the potential benefit justifies the potential risk to the newborn.

II. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Conclusions

Both the pivotal studies **IP631-003** and **IP631-005** were adequate and well-controlled studies conducted in the US. Both provide substantial evidence of efficacy in the primary and key secondary efficacy variables. Study **MP94D2.14** also provides support of effectiveness, whereas study **MP94D2.15** provides marginal support of effectiveness only in key secondary efficacy variables.

The improvement in the signs and symptoms of overactive bladder (OAB) is supported by data suggesting an associated improvement in health-related quality of life.

The proposed indication therefore is well supported by the efficacy data.

B. Method of Efficacy Review

The reviewer's basic approach to the efficacy review involved:

- Review of the proposed indication, protocols, regulatory and scientific background
- Identification and review of the well-controlled studies to support the indication
- Conduct of a detailed review of each study for efficacy
- Detailed discussions and interactions with Biometrics
- Generate conclusion regarding efficacy from the pivotal and supporting studies

C. List of Studies, Designs, Population and Efficacy Variables

The following studies were analyzed individually in detail during the review process:
IP631-003 - a Pivotal study
IP631-005 - a Pivotal study
MP94D2.14 - a Supporting Study
MP94D2.15 - a Supporting Study

All four trials (**IP631-003, IP631-005, MP94D2.14 and MP94D2.15**) were randomized, multi-center, double-blind, placebo-controlled, parallel group studies of efficacy and safety conducted in the US (IP631-003 and IP631-005) for a duration of 12 weeks and in Europe (MP94D2.14 and MP94D2.15) conducted for a duration of 3 to 4 weeks. There was one 9-month open label extension.

- Both the studies IP631-003 and IP631-005 collected urinary data on toilet void frequency, the urgency severity associated with each toilet void, and the number of incontinence episodes for 7 full days prior to the baseline, the Week 1, the Week 4, and the Week 12 visits. Data for volume voided was collected for 2 full days prior to these same visits.
- Study MP94D2.14 collected urinary data on the number of toilet voids, number of incontinence episodes, volume voided, and "frequency of urgency" for 2 full days prior to the baseline visit as well as 2 days per week during each week of treatment period (i.e., during Weeks 1, 2 and 3)

- Study MP94D2.15 collected urinary data for toilet void frequency, number of incontinence episodes, and number of diaper changes per day from Day 10 (the baseline Visit) to Day 21 (the end of the treatment period)

Key study entry criteria for all 4 trials included:
1. Male and female patients 18 years and older
2. Patients with OAB for more than 6 months
3. Frequency of micturitions >70 per week, symptoms of urgency, and urge incontinence of at least 7 episodes per week
4. Maximum cystometric bladder capacity < 350 ml at the start of trial.

In study **IP631-003**, a total of 523 patients were randomized to receive trospium chloride 20mg or the placebo [262 to trospium (75 M and 186 F) and 261 to placebo]. In study **IP631-005**, a total of 658 patients were randomized (329 to trospium and 329 to placebo). In study **MP94D2.14**, a total of 309 patients were enrolled; 210 (68%) were treated with trospium and 99 (32%) received placebo. In study **MP94D2.15**, a total of 232 patients were randomized; 76 patients received trospium, 77 patients received a comparator drug, and 79 patients received placebo.

The **key end points** presented from the patient urinary diary data included:
1. Toilet void frequency (urinary frequency)
2. Urinary incontinence episodes
3. Volume voided
4. "Urgency frequency" (in study MP94D2.14) and "urgency severity" (in studies IP631-003 and IP631-005).

D. Statistical Analysis Plan (SAP)
- All statistical analysis plans were finalized prior to treatment assignment
- All randomized subjects with a baseline measurement were included in the efficacy analysis
- Last-observation-carried-forward (LOCF) approach was used for any missing data
- Analysis of variance (ANOVA) was planned as the test of treatment differences. The reader is referred to the Biometrics review for more details regarding the SAP and actual analyses conducted.

E. Efficacy Results

Table 1. Summary of Baseline Patient Urinary Data for Studies IP631-003, IP631-005, MP94D2.14 and MP94D2.15

Study	IP631-003		IP631-005		MP94D2.14		MP94D2.15	
	Tcl	**Pla**	**Tcl**	**Pla**	**Tcl**	**Pla**	**Tcl**	**Pla**
Total N	**262**	**261**	**323**	**325**	**210**	**99**	**76**	**79**
Toilet Voids/24 hrs (n)	253	256	323	325	82	36	71	74
Baseline	12.74	12.93	12.94	13.17	13.0	10.9	11.7	12.2
Incontinence Episodes/24hrs (n)	253	256	323	325	33	24	43	43
Baseline	4.37	4.77	3.84	3.90	3.9	3.6	3.2	2.7
Volume Voided (ml)/toilet void (n)	248	253	319	320	77	35	73	72
Baseline	155.1	156.6	154.8	154.6	142.9	135.3	128.1	126.4
Urgency	253	256	323	325	50	28	Not collected	
Baseline	1.77	1.77	1.79	1.75	14.9	9.9		

The baseline mean values for toilet voids per 24 hours and incontinence episodes per 24 hours were similar between treatment groups within each study. Volume voided per toilet was collected in all four studies, however, in study MP94D2.14, the urgency data was collected as "urgency frequency", while in studies IP631-003 and IP631-005, the data was collected using a 4-point severity score.

Reviewer's Comment

In the opinion of this reviewer, the baseline urinary data for patients in study IP631-003 and IP631-005 were quantitatively similar to the baseline data for the patients in the two European trials. In these European studies, study MP94D2.15 provides marginal support for surrogate end points, but study MP94D2.14 provides further evidence of efficacy for trospium in the treatment of patients with overactive bladder (OAB).

Tables 2 and 3 below summarize the key efficacy results for all 4 studies. In these tables "Tcl" refers to trospium chloride and "Pla" to Placebo.

Table 2: Summary of change from baseline for key efficacy variables

Study	Number of Toilet Voids per 24 hrs		Number of Incontinence Episodes /24 hrs		Volume Voided (ml) Per toilet void		Urgency	
IP631-003	**Tcl** N=253	**Pla** N=256	**Tcl** N=253	**Pla** N=256	**Tcl** N=248	**Pla** N=253	**Tcl** N=253	**Pla** N=256
Week 1	-1.18	-0.81	-1.40	-1.35	19.88	6.55	-0.11	-0.01
Week 4	-2.20	-1.07	-2.02	-1.87	29.96	8.45	-0.18	-0.06
Week 12	-2.37	-1.29	-2.20	-1.98	32.14	7.72	-0.22	-0.04
IP631-005	**Tcl** N=323	**Pla** N=325	**Tcl** N=323	**Pla** N=325	**Tcl** N=319	**Pla** N=320	**Tcl** 323	**Pla** 325
Week 1	-1.42	-0.96	-1.62	-0.93	29.23	6.05	-0.09	-0.01
Week 4	-2.34	-1.55	-2.14	-1.60	39.50	9.45	-0.19	-0.04
Week 12	-2.67	-1.76			35.59	9.44	-0.21	-0.02
MP94D2.14	**Tcl** N=82	**Pla** N=36	**Tcl** N=33	**Pla** N=24	**Tcl** N=77	**Pla** N=35	**Tcl** N=50	**Pla** N=28
Weeks 1,2,3	-3.0	-0.6	-1.2	-1.2	36.4	9.4	-3.3	-2.4
MP94D2.15	**Tcl** N=71	**Pla** N=74	**Tcl** N=43	**Pla** N=43	**Tcl** N=73	**Pla** N=72	**Tcl**	**Pla**
Week 3	-2.60	-1.75	-2.3	-1.6	35.63	14.80	NC	NC

Table 3: Overview of p-values results for key urinary diary data

Study	Toilet Void Frequency	Incontinence Episodes	Volume Voided	Urgency
IP631-003 (12 Weeks)	P<0.001	P=0.011	P<0.001	P=0.001
IP631-005 (12 Weeks)	P<0.001	P=0.0001	P<0.001	P=0.001
MP94D2.14 (3 Weeks)	P=0.03	NS	P=0.008	NS

NS - Results not significant, NC - Results not collected

Overall, the magnitude of effect was consistent for the key diary data variables from the two pivotal studies (**IP631-003 and IP631-005**) and for the two European studies (**MP94D2.14, and MP94D2.15**).

All 4 controlled studies presented in the tables above showed improvement (decreases) in number of toilet voids per 24 hours. For 3 of the 4 studies, the improvement was statistically significant compared with placebo (i.e., IP631-003, IP631-005 and MP94D2.14). For study MP94D2.15 the improvement demonstrated was statistically marginal with a p value of approximately 0.05.

For the incontinence episodes endpoint, 3 of the 4 controlled studies showed a reduction in the number of incontinence episodes per 24 hours (IP631-003, IP631-005 and MP94D2.15). For the pivotal studies (IP631-003 and IP631-005), the improvement in

incontinence episode frequency was statistically significant compared with placebo. For study MP94D2.15, the improvement was numerically greater for trospium compared to placebo. For study MP94D2.14, there was no difference between treatment groups.

All four controlled studies collected data on volume voided per toilet void and all demonstrated that trospium chloride provided statistically significant improvements in increasing volume voided per toilet void when compared with placebo.

In addition, 3 of the 4 controlled studies collected data on urgency. Study IP631-003 and IP631-005 collected urgency as a 4-point severity score and the results from these studies showed a statistically significant improvement (a decrease) in the 4-point urgency severity scale compared to placebo. Study MP94D2.14 showed a greater reduction in urgency frequency for the trospium group compared to the placebo group.

Urodynamic measurement data were provided as physiologic evidence to support the patient urinary diary data in demonstrating the efficacy of trospium. In one of the studies (MP94D2.14), sponsor analyzed urodynamic data, showing a significant increase for the key urodynamic variables of maximum cystometric bladder capacity and volume at first unstable contraction.

A "global assessment of efficacy" question was provided as further support of improved symptoms. Both European studies (MP94D2.14 and MP94D2.15) collected the global assessment of efficacy as assessed by the investigator. In these studies, the investigator assessment of efficacy showed more trospium-treated patients with a marked improvement of symptoms compared to placebo-treated patients. The global assessment of efficacy by the patient for these same studies was consistent with the investigator assessment of efficacy.

F. Efficacy Conclusions

The pivotal studies **(IP631-003 and IP631-005)** showed statistically significant changes from baseline in both traditional primary endpoints (number of toilet voids [urinary frequncy] and number of incontinence episodes) and in the key secondary endpoints when compared to placebo for a period of 12 weeks.

Study **MP94D2.14** provided supporting evidence of efficacy in both primary and key secondary endpoints when compared to placebo and for urodynamic parameters. Study **MP94D2.15** provides marginal support for trospium chloride 20-mg given twice daily in patients with overactive bladder from detrusor instability and/or urge incontinence.

Therefore, in the opinion of this reviewer, the effectiveness of trospium was well-supported by results from the controlled studies.

III. Integrated Summary of Safety (ISS)

A. Brief Statement of Conclusions

The adverse event profile of trospium chloride appears to be similar to that of other potent anticholinergic drugs. Dry mouth, abdominal pain, constipation and headache were the most frequently reported events in the pivotal studies (**IP631-003 and IP631-005**) and in the two supporting studies (**MP94D2.14 and MP94D2.15**). The other less frequently reported but clinically significant adverse events associated with trospium were non-cardiac chest pain and urinary retention in studies IP631-003 and IP631-005, urinary retention in study MP 94D2.14, and abnormal vision and accommodation in study MP94D2.15. All chest pain cases were individually analyzed and none appeared to reflect active myocardial ischemia.

No hepatotoxicity was reported in any trial of trospium chloride, although there were several patients with mild increases in serum transaminases. There was no determination of a direct association between increases in transaminases and trospium. There has been no evidence of any syncope or renal toxicity associated with trospium.

It has been determined that the drug elimination in patients with severe renal insufficiency is reduced; therefore, dose reduction in that group has been instituted.

No apparent QT safety signal was identified among patients in studies IP631-003 and IP631-005. **Study IP631-010** was specifically designed and conducted to study the effect of trospium chloride on cardiac repolarization. The study was adequately powered and included a positive control, as recommended in the FDA draft guidance document. This trial, in evaluating the effects of trospium chloride at markedly supratherapeutic doses (100mg twice daily), showed that trospium does not effect cardiac repolarization or conduction. However, there was evidence of t-wave inversion possibly related to tachycardia in asymptomatic patients during this trial, especially in the supratherapeutic group. This t-wave inversion, in presence of tachycardia, did not translate into a conclusive clinically meaningful diagnosis. Therefore, it appears to pose no specific cardiac risk.

In view of all the facts summarized above, **trospium chloride is considered to be safe** at a dose of 20mg twice daily given orally to patients with OAB.

2. Description of Patient Exposure and Demographics

The **pivotal study IP631-003** was conducted at 51 US clinical sites and 531 patients with OAB were enrolled. A total of 523 patients received study treatment (trospium 262 and placebo 261) for 12 weeks.

The **U.S. open-label extension period** was designed to further explore the long-term efficacy and safety effects of trospium chloride in reducing urinary frequency and other symptoms associated with OAB following the initial 12-week treatment period.

In pivotal study **IP631-005**, a total of 658 patients (trospium 329 and placebo 329), received study treatment. The patient population was predominantly female and mean age group was 61 years.

Study **MP94D2.14** was completed at multiple sites in Europe. In this study, 309 patients with OAB due to detrusor instability were enrolled and received at least one dose of study medication. The cohorts used to analyze safety and the ITT efficacy were identical during this 21-28 day trial.

Study **MP94D2.15** was also completed at multiple sites in Eastern Europe. In this study, a total of 232 patients with OAB were randomized to receive at least one dose of the study medication. Again, the cohorts used to analyze safety and ITT efficacy were identical during this 23-day trial.

3.Method of Integrated Safety Review

The reviewer conducted analysis of safety from each of the four listed trials that included the following:

-Deaths
-Serious adverse events
-Medically significant adverse events
-Overall treatment emergent adverse events
-Discontinuation of study medication due to adverse events
-Laboratory findings
-Vital signs and ECG findings
-Special safety concerns
-Anticholinergic side effects

In addition, the reviewer analyzed the sponsor's integrated summary of safety for the same parameters as described in the original NDA, the 4 month safety update, and the update from 23-Feb-2004 that accompanied the study report for study IP631-003.

A. Deaths

As of the submission of this NDA and the safety updates thereafter, a total of 10 deaths have been reported in all placebo and active controlled studies. None of the SAE's resulting in death in these studies were judged by the investigator to be related to the study medication.

There was one patient in the trospium group of both studies IP631-003 and IP 631-005, who experienced an adverse event leading to death. There were no deaths reported in the other two supporting studies (MP94D2.14 and MP94D2.15).

Patient 50-6247 (IP631-003)

An 81 year old Caucasian male with significant past medical history of myocardial infarction in 1985, coronary artery bypass surgery in 1994, hypercholestrolemia and

glaucoma since 1985, was hospitalized on day 57 after initiation of the study medication for hemorrhagic stroke. CT scan of the head revealed left parieto-occipital intracranial hemorrhage with surrounding edema and mild mass effect. A carotid duplex scan showed a 15% occlusion of both internal carotids and antegrade flow in the vertebral arteries bilaterally. MRI of the brain revealed intraparenchymal hemorrhage in the left temporal and left parietal areas with mild intraventricular blood. The hemorrhage was attributed to pre-existing amyloid angiopathy with hypertensive hemorrhage. The study drug administration was permanently discontinued on Day 57 due to the occurrence of this event. The patient stayed stable for next 11 days and was transferred to a nursing home where he died later on Day 125 [redacted]. Cause of death as stated in the death certificate was a consequence of cerebral hemorrhage. The sponsor/investigator assessed the hemorrhagic stroke as remotely related to the study medication.

Patient 13-6313 was a 73-year-old Caucasian male with significant past medical history of congestive heart failure, hypertension, ruptured intestines, colostomy reversal (1997 and 1998), and obesity. On Day 22 (of being on study medication), the patient developed severe nausea and vomiting, abdominal pain, and became weak, dehydrated, and was unable to get out of bed. On Day 23, he was admitted to the hospital and diagnosed with a bowel obstruction. ECG showed normal sinus rhythm, PVC's and right bundle branch block. Laboratory test evaluation revealed renal insufficiency. Chest x-ray was normal. The patient was treated with meperidine, hydroxyzine, metoclorpramide, dicyclomine, and famotidine. He also received topical nitroglycerin paste and verapamil. Cardiac and surgical consults were obtained. During the evening of Day 23, the patient developed shortness of breath and decreased blood pressure. He was diagnosed with myocardial infarction. On Day 24, the patient experienced cardiac arrest and subsequently died.

Reviewer's Comment: ***This reviewer agrees with the assessment stated in this submission. It is highly unlikely that the study medication could have caused or led to hemorrhagic stroke in patient 50-6247 (IP631-003) given that the patient had a relevant pre-morbid medical condition. However, in the case of patient 13-6313 (IP631-005) a cascade of events from constipation, post-op abdominal adhesions and intestinal obstruction could possibly have contributed to MI that resulted in death.***

B. Serious Treatment Emergent Adverse Events (serious TEAE's)

Study IP631-003

In this pivotal study, sponsor reported 15 patients [trospium 9 patients (3.4%) and placebo 6 patients (2.3%)] who experienced at least 1 serious TEAE as shown in the Table 4 below.

Study IP631-005

In this pivotal study, sponsor reported a total of 18 patients [trospium 12 (3.6%), placebo 6 (1.8%)] who experienced at least 1 serious TEAE as shown in Table 5 below.

Sponsor believes that the serious TEAE's reported during these two pivotal studies were serious by regulatory definition, but were not life-threatening, other than the single patient in the trospium group of each study that died. All these serious events were assessed by the investigator as remotely or possibly not related to the study medication.

There were no serious treatment emergent adverse events reported in either of the two supporting studies MP94D2.14 and MP94D2.15.

Table 4. All Serious TEAE's in Study IP631-003

	Number of Patients (%)	
	Placebo N=261	Trospium N=262
Patients with at least 1 TEAE	138(52.9)	171(65.3)
Patients with at least 1 serious TEAE	6(2.3)	9(3.4)
Death	0(0.0)	1(0.3)

Table 5. All Serious TEAE's in Study IP631-005

	Number of patients (%)	
	Placebo N=329	Trospium N=329
Patients with at least 1 TEAE	153(46.5)	196(59.6)
Patients with at least 1 serious TEAE	6(1.8)	12(3.6)
Death	0(0.0)	1(0.3)

C. Other Medically Significant Adverse Events

There were no other medically significant adverse effects in trospium group in the pivotal studies IP631-003 and IP631-005 other than those reported above. However, there were 3 patients (trospium 2 and placebo 1) in study MP94D2.14 who experienced significant adverse effects i.e., one of the two patients on trospium (#278) developed a neurological event resulting in hemiparesis. This patient was hospitalized and study medication was discontinued. The causality was determined by the investigator as being not related to tropium. The second patient (#283) developed urinary and fecal retention. The study medication was withdrawn and the symptoms improved with minimal medical intervention. The causality assessment by the investigator was that the event was not related to trospium. There were no significant adverse effects reported in other supporting study MP94D2.15.

D. Discontinuation of Study Medication due to Adverse Events

Study IP631-003

Table 6 summarizes the adverse events during study IP631-003 that either led to discontinuation of study medication or led to temporary interruption of study medication, or required dose reduction of study medication.

Table 6: Discontinuations due to adverse events in Study IP631-003

	Number of patients (%)	
	Placebo N=261	**Trospium N=262**
Lead to discontinuation of study medication	15(5.7)	23(8.8)
Lead to temporary interruption of study medication	8(3.1)	16(6.1)
Required dose reduction of study medication	0(0.0)	1(0.4)

Study medication was permanently discontinued due to TEAE's in 38 patients in this pivotal study, [(trospium 23 patients (8.8%) and placebo 15 patients (5.7%)]. The most common TEAE's that led to discontinuation of the study medication occurred in the gastrointestinal and urinary system. i.e., dry mouth, constipation, abdominal pain and urinary retention.

TEAE's in this study that led to temporary interruption of the study medication were non-cardiac chest pain and urinary retention. There was one patient in the trospium group who experienced oliguria on Day 4 on being on study medication. This led to dose reduction from 20mg BID to 20mg QD for 4 days. The decreased urine output resolved by Day 6.

Study IP631-005

Table 7: Discontinuations due to adverse events in Study IP631-005

	Number of patients (%)	
	Placebo N=329	**Trospium N=329**
Lead to discontinuation of study medication	15(4.6)	24(7.3)
Lead to temporary interruption of study medication	12(3.6)	13(4.0)
Required dose reduction of study medication	2(0.6)	1(0.3)

Study medication was permanently discontinued due to TEAE's in a total of 39 patients in this study [trospium 24 (7.3%) and placebo 15 (4.6%)]. The most common TEAE's that led to discontinuation of study medication occurred in the GI system, i.e., dry mouth and constipation. None of these events required any significant medical intervention.

Study medication was temporarily interrupted due to TEAE's in a total of 25 patients [trospium 13 (4.0%) and placebo 12 (3.6%)].

Studies MP94D2.14 and MP94D2.15
There were no adverse events reported in these two supporting studies that led to discontinuation or reduction in dose of the study medication.

E. Overall Treatment Emergent Adverse Events (TEAE's)

Study IP631-003
The most common adverse events reported by patients in either treatment group during study IP631-003 were dry mouth, constipation, abdominal pain, headache, chest pain and urinary retention as demonstrated in Table 8 below. The data is presented without reference to causality.

Table 8. Table of overall adverse events from Study IP631-003

Adverse event	Trospium N=262	Placebo N=261
Total patients with at least one event	**138(52.9%)**	**171(65.3%)**
Dry Mouth	57(21.8%)	17(6.5%)
Constipation	25(9.5%)	10(3.8%)
Headache	17(6.5%)	12(4.6%)
Abdominal Pain	8(3.1%)	3(1.1%)
Chest Pain	6(2.3%)	1(0.4%)
Urinary Retention	6(2.3%)	1(0.4%)

The most common adverse events presented in the table above, dry mouth and constipation occurred in > 5.0% of trospium patients. This is consistent with the anticholinergic effect of trospium chloride. However, there are two other TEAE's i.e., chest pain and urinary retention seen at a higher incidence in the trospium group and these two AE terms were analyzed separately.

Chest pain
There were a total of 7 patients who experienced chest pain during this trial [trospium 6 patients (2.3%) and placebo 1 patient (0.4%)]. Of the 6 patients on trospium who developed chest pain, 1 patient experienced severe chest pain, 2 patients experienced chest pain requiring hospitalization, and 1 patient experienced chest pain that led to discontinuation of study medication.

For 4 out of 6 patients on trospium who experienced chest pain, sponsor believes that there was no relationship to the study drug. The remaining two patients on trospium who experienced chest pain had prior co-morbid cardiovascular disease. The investigators for these two events could not rule out a possible relationship to study drug.

Reviewer's comment
This reviewer agrees with the sponsor's assessment that none of the six patients on trospium who experienced non-cardiac chest pain in this study were due to active myocardial ischemia

Urinary Retention
A total of 7 patients [trospium 6 patients (2.3%) and placebo 1 patient (0.4%)] experienced urinary retention during this trial. According to the sponsor, none of these urinary retention events were severe or serious, but in 4 of 6 patients who experienced urinary retention among the trospium group, the study medication had to be discontinued.

The sponsor believes that 5 out of 6 patients who experienced urinary retention while on trospium chloride were possibly related to the study medication.

Reviewer's Comment
This reviewer agrees with the sponsor's assessment that urinary retention/post void fullness in 5 of these 6 patients was probably related to treatment with trospium. Nevertheless, it is important to note that all of these patients had pre-existing multiple medical illnesses that could have contributed to urinary retention. For example, approximately half of patients on trospium who developed urinary retention also had bladder outlet obstruction due to pre-existing BPH (in men).

Study IP631-005

Table 9. Table of overall adverse events from Study IP631-005 (all-causality)

Adverse event	Trospium N=329	Placebo N=329
Total patients with at least one event	**138(52.9%)**	**153(46.5%)**
Dry Mouth	65(19.8%)	17(5.2%)
Constipation	36(10.9%)	19(5.8%)
Headache	18(5.5%)	15(4.5%)
Urinary Retention	2(0.6%)	1(0.3%)
Chest Pain	3(0.9%)	0(0.0%)
Angina Pectoris	2(0.6%)	0(0.0%)
Myocardial Infarction	3(0.9%)	0(0.0%)

Again, the most common adverse events presented in the table above (e.g. dry mouth, constipation, headache and urinary retention) seem to be consistent with the potent anti-cholinergic effect of trospium chloride. However, the adverse event terms chest pain, angina, and myocardial infarction seen in patients on trospium were individually analyzed and are summarized below:

Chest pain
None of the three patients who experienced non-cardiac chest pain experienced events consistent with active myocardial ischemia.

Angina
Both the patients who experienced anginal pain while being on trospium chloride had a past medical history of coronary artery disease (CAD) and multiple existing risk factors related to coronary artery disease. One of the two patients, #42-642, who had a subsequent non-Q wave MI, was diagnosed with 3 vessel disease and treated with CABG on Day 84, and later recovered. None of the events listed as "angina" were serious by definition and none required any further medical intervention. Both these cases were determined as remotely related to the study medication by the investigator.

Myocardial infarction
Three patients with multiple underlying medical/cardiac conditions and extensive risk factors for cardiac ischemia experienced myocardial infarction. Two of the three were judged as remotely related to the study medication. In the third patient (**#13-6313**), a 73 year old male with prior abdominal surgery, extensive abdominal adhesions, and short gut syndrome, intestinal obstruction was diagnosed on Day 22 leading to hospitalization. The patient subsequently experienced a myocardial infarction resulting in death a day later.

Reviewer's Comment
This reviewer agrees with the investigator that there were pre-existing cardiac risk factors in all three patients who experienced a myocardial infarction. However, patient 13-6313 who died secondary to a MI while being hospitalized, had significantly relevant medical and surgical risk factors that could have contributed to his death (i.e., pre-existing post-surgical abdominal adhesions and short bowel syndrome).

Therefore, in the opinion of this reviewer trospium chloride should be used with caution in patients with a history of bowel obstruction as evident from case 13-6313 where the bowel obstruction possibly contributed to a cascade of ultimately fatal events.

Study MP94D2.14

Table 10. Table of overall adverse events from Study MP94D2.14 (all-causality)

Adverse Events	Trospium	Placebo
Gastrointestinal*	15	1
Urinary Disorders	10	3
Urinary Retention	1	3
Dizziness and Headache	4	2
Respiratory Symptoms**	4	0
Exanthema &Visual Abnormality	1	2

*Includes dry mouth, constipation and diarrhea
**Includes dyspnea, cough and bronchitis

There were 15 patients in the trospium group who experienced mild adverse events that were mostly gastrointestinal. Six patients experienced dry mouth, two had constipation and three had diarrhea. In two of these patients, #209 and #56, medication was discontinued due to prolonged GI symptoms. There was also one patient in the trospium group who experienced mild urinary retention that resulted in discontinuation of study drug and one other patient who was found to have exanthema and mild visual disturbance that resolved spontaneously.

The other adverse events reported were UTI, dizziness, headache and mild respiratory symptoms (i.e., dyspnea, cough and bronchitis).

Study MP94.D2.15

There were a total of 106 adverse events (AE's) observed in 63 patients in this study. A total of 26 patients (34.2%) treated with trospium chloride reported 39 adverse events compared to 25 patients (32.5%) reporting an adverse event in active comparator group and 12 patients (15.2%) experienced adverse event in the placebo group.

The most affected organ disorders reported were gastrointestinal (22%). The most frequently reported single AE from this system was dry mouth in 48 patients (20.7%), 22 patients treated with trospium chloride and 21 patients treated with active comparator.

Other adverse events reported with trospium, although not frequent, were abnormal vision (2.6%) and accommodation (2.6%), which were comparable to the placebo group (0.9% and 1.7%, respectively).

Reviewer's Comment

It is the impression of this reviewer that the adverse events experienced by the patients on trospium during this trial were mild and mostly gastrointestinal, typical adverse events seen with anticholinergic medications. In this study, all AE's resolved without intervention.

F. Laboratory Evaluations

Study IP631-003

Based on the study protocol, routine laboratory testing was conducted at screening and day 84 (Week 12) visits during this trial. Hematology, chemistry, and urinalysis data were reviewed for changes that occurred from baseline to on-treatment. In addition, laboratory data were analyzed using predefined criteria to identify potentially clinically significant (PCS) abnormal laboratory values. There were no significant findings.

Study IP631-005

The number of patients who met potentially clinically significant (PCS) criteria for the hematology and serum chemistry laboratory data was similar for the trospium and placebo groups. Although there were more patients in the trospium group who met PCS criteria for urinary WBC's when compared with the placebo group, the differences in the UA findings did not translate into a clinically meaningful difference.

Reviewer's Comment
It is the opinion of this reviewer that both hematology and serum chemistry values were similar between trospium and placebo groups and a mild increase in epithelial cells and WBC's in patients, other than those suffering from clinical UTIs, did not translate into a clinically meaningful differences. (For more details in regard to lab data for the pivotal studies, the reader is referred to appendix B).

Study MP94D2.14
There were no treatment related relevant changes seen in any laboratory values during this trial.

MP94D2.15
None of the patients in trospium or placebo group during this trial showed any abnormal values, which could translate into a clinically meaningful result. There were four patients on tolterodine who showed mild increase in creatinine level compared to placebo and one patient showed a mild decrease in platelets. This patient was enrolled with a PMH of thrombocytopenia.

G. Vital Signs and ECGs

Study IP631-003
Vital signs (i.e., blood pressure [systolic and diastolic] and pulse rate) and ECGs were measured at screening, baseline, at Day 8 (Week 1), at Day 28 (Week 4) and at Day 84 (Week 12) during this pivotal trial.

Data on **vital signs** was found to be similar in both trospium and placebo groups most only a modest increase in heart rate in the trospium group.

ECGs
In the analysis using Fridercia's correction, patients in trospium group (in this study) did not show a higher percentage of abnormal QTc >450 msec compared with the placebo group. As demonstrated earlier, ECGs demonstrated that trospium was shown to be associated with a heart rate increase of approximately 3bpm from baseline. This increase in heart rate did not translate into a clinically meaningful change.

Study IP631-005
The number of patients who met potentially clinically signficant criteria for the vital signs and ECG data was similar for both trospium and placebo groups in this study.

Although, the number of patients was small, there were more patients in the trospium group who met PCS criteria for high heart rate (>100bpm and an increase from baseline >15 bpm) when compared with the placebo group. There was 1 patient in the trospium group who met PCS criteria for high heart rate of >120 and an increase >15 bpm.

The mean change in QTcF interval from baseline in the trospium group was -0.9 msec and in the placebo group was 3.5 msec. There was 1 patient in the trospium group who had QTcF interval >500 msec that had increased by >60 msec from baseline. But this patient showed no clinical signs or symptoms associated with the increased QTcF interval which resolved at endpoint.

Reviewer's Comment
It should be noted that no apparent QT safety signal was identified among patients in studies IP631-003 and IP631-005. Study IP631-010 was specifically designed and conducted to study the effect of trospium chloride at maximum tolerated dose levels on cardiac repolarization. The study was adequately powered and included a positive control, as is recommended in the FDA guidance document. This trial (IP631-010), which evaluated the effects of trospium chloride at maximum tolerated dose levels, showed that trospium did not effect cardiac repolarization or conduction. However, there was evidence of t-wave inversion in otherwise asymtomatic patients seen during this study. The clinical significance of this finding in this subgroup may be related to an increased heart rate associated with trospium chloride, or some other non-specific and not clinically relevant etiology.

Study MP94D2.14
No clinically relevant changes were seen in the vital signs data during this trial.

Study MP94D2.15
During this trial, trospium was shown to be associated with a median increase of 1.5 bpm in the heart rate which did not translate into a clinically meaningful change.

Reviewer's Comment
In the opinion of this reviewer, caution should be exercised by patient's 65 years of age and older to avoid taking combination of anticholinergic drug products, which otherwise could result in an increase in tachycardia and palpitations.

H. Special Safety Concerns
It is the opinion of this reviewer that trospium chloride, although a mild anticholinergic drug, should be used with caution in patients with severe renal insufficiency. Since trospium chloride has been shown to be actively secreted and excreted via kidneys resulting in a 2-fold increase in plasma concentration in those patients with severe renal insufficiency.

Trospium chloride should also be used with caution in patients with past medical history of ileus or intestinal obstruction.

Caution should also be exercised in patients greater then or equal to 75 years of age, in whom a more pronounced anticholinergic effect has been demonstrated (i.e., dry mouth, constipation, dyspepsia and urinary retention) when compared to younger age groups.

Reviewer's Comment
In the opinion of this reviewer, if prescribers are considering trospium chloride for use in patients with renal insufficiency, it may be essential to calculate the creatinine clearance before establishing the actual dose. For example, the dose in severe renal insufficiency (creatine clearance <30mL/min) is once daily to be taken at night, since trospium has exhibited diurnal variation. (i.e., if taken at night, there is less bioavailability than if taken during the day).

Secondly, it may be necessary to decrease the frequency of this medication to once daily in the elderly patients 75 years of age and older depending on tolerability, to reduce anticholinergic adverse events in this population.

H. Anticholinergic Side Effects

The most common anticholinergic adverse events associated with trospium use were related to gastrointestinal system i.e., dry mouth, abdominal pain and constipation. None of these required any intervention at any point during the two pivotal trials.

The other important adverse events of concern were chest pain, myocardial infarction and urinary retention. Chest pain was reported only in the pivotal studies IP631-003 and IP631-005, but patients in both pivotal and supporting studies experienced urinary retention. The chest pain was determined as non-ischemic by the investigators in all patients who experienced chest pain. The reviewer agrees. Myocardial infarction occurred in three patients during the study IP631-005. Two of the three were determined not related to the study medication by the investigators. The third patient had a cascade of events ranging from intestinal obstruction to MI and later cardiac arrest that resulted in death. Other than this patient (#13-6313), none of the events were serious or required any further intervention.

Patients who developed urinary retention, although a recognized side effect of anticholinergics, were found to have outlet obstruction from BPH in half of the involved patients (who were men). None of these patients required hospitalization or any serious intervention and all patients had full recovery.

There have been two cases of vertigo reported in phase I PK studies (MP94D2.08 and MP94D2.11). Although, both of these cases were determined as unrelated to study medication by the investigator, trospium chloride should be discontinued if such an event persists.

Safety Conclusions

1. **Although, trospium chloride at a dose of 20-mg twice daily in patients with OAB is effective and safe, it should be used with caution in patients with severe renal impairment. A creatinine clearance should be obtained for dosing before administering the drug in such patients.**
2. **It should also be used with caution in patients with history of pre-existing ileus or intestinal obstruction.**
3. **In order to avoid increased anticholinergic effects in patients 75 years of age and older, trospium may be down-titrated for less frequent use (i.e., once daily at night to obtain the diurnal effect of trospium.**
4. **Trospium should be discontinued in patients who develop prolonged urinary retention unrelieved by temporary cessation of medication.**

Appendix A. Medical Officer's Review of Pivotal Study IP 631-003
Table of Contents

1.0. INTRODUCTION

Overactive bladder (OAB) is estimated to affect between 50 and 100 million people worldwide and is ranked among the ten most common chronic medical conditions.

Overactive bladder (OAB) is characterized by urinary frequency and urgency, with or without urge incontinence (UI). Urinary incontinence (UI) is characterized by an involuntary loss of urine that is objectively demonstrable, often leading to social difficulties and medical (hygienic) consequences. Urinary incontinence frequently results from disturbances of the urine storage phase of the detrusor muscle or failure to empty urine. Abnormalities of the bladder, sphincter, spinal cord, or brain may result in urinary incontinence (UI).

The most common types of urinary incontinence (UI) include urge incontinence, stress incontinence and mixed urinary incontinence (UI) (i.e., combination of urge and stress incontinence). While symptomatology of UI associated with OAB is predominantly associated with urgency, mixed incontinence occurs primarily in women, particularly following childbirth, and accounts for approximately one-third cases of UI in females.

The treatment options include behavioral modification techniques, such as timed voiding; bladder drills and prompted voiding, pelvic floor exercises, pharmacological therapy, and surgery. The aim for the clinical intervention should target medical, hygienic and social issues, since OAB affects one's quality of life impacting on physical, social, emotional and mental health.

Trospium chloride was first introduced as a spasmolytic agent in 1967 in Germany. It is currently approved in several European countries in a dose of 20mg for specific therapeutic indications including urinary frequency, nocturia, and urge incontinence.

Trospium chloride is a quaternary ammonium derivative of atropine with anticholinergic properties and peripheral muscarinic like activity, proposed for the treatment of symptoms of OAB. Trospium chloride antagonizes the effect of acetylecholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing smooth muscle tone, that enables the detrusor muscle to relax, thus inhibiting evacuation of the bladder.

Trospium chloride is slowly absorbed following an oral ingestion with maximum plasma concentration that occurs approximately 5 hours post dose. The mean absolute bioavailability is approximately 10%. Administration with high fat meal results in reduced absorption, with AUC and Cmax values 70-80% lower than those obtained when trospium is administered 1 hour prior to food.

Trospium chloride [including this study (IP 631-003)] has been studied in 32 clinical trials involving over 2700 patients and subjects. The most common dose used was 20-mg twice daily.

2.0 Study Objectives

The objective of this study was to determine the effects of 20 mg of trospium chloride versus placebo given twice daily for overactive bladder associated with predominant urge incontinence over a 12- week treatment period.

3.0 Investigational Plan

3.1 Efficacy Variables

3.1.1 Primary Efficacy

The **co-primary efficacy** variables are:

1. **Change in average number of toilet voids per 24 hours**
2. **Change in average number of urge incontinence episodes per 24 hours.**

The primary efficacy analyses was focused on the change from baseline to Day 84 (Week 12) visit.

The primary efficacy variables are based on data collected over 7 days prior to the baseline, Day 8, Day 28, and Day 84 visits. The data is generated from the record of patient urinary diaries.

Reviewer's Comment:
Primary efficacy variables are acceptable

3.1.2 Secondary Efficacy

The secondary efficacy variables assessed in this trial are

1. **Effect on volume (i.e., an increase in average volume voided**
2. **Effect on urgency severity (i.e., decrease in average urgency severity)**

The secondary efficacy assessments were collected over 7 days prior to the baseline, Day 8, Day 28, and Day 84 visits using data recorded in patient diaries. Volume voided was collected for 2 full days prior to each visit.

Reviewer's Comment:
Secondary efficacy variables are acceptable. It is not yet clear whether the 4-point urgency severity scale is adequately validated.

3.2 Study Design and Randomization

This was a multi-center, randomized, double blind, placebo controlled, parallel group trial conducted at sites all across the United States, in patients with overactive bladder (OAB). Patients were randomized on 1:1 basis to receive either placebo or trospium chloride 20 mg oral twice daily. The randomization was stratified by the mean baseline number of micturitions (i.e., toilet voids) per 24 hours. The data was collected via the patient daily diaries over seven days. Randomization treatment assignment was accomplished with the use of an interactive voice response system (IVRS). Using IVRS, patients randomized were required to have > 10 micturitions per day over a seven day period in addition to > than 7 urge incontinence episodes over a period of seven days.

Once the randomization process was completed, the IVRS provided each site with a four-digit study medication kit number. A combination of both the kit number and the site number became patient's identification number.

Reviewer's comment
The study design is acceptable and the randomization process using interactive voice response system (IVRS) is appropriate.

3.3 Dosing Schedule
Each patient was instructed to receive one tablet of study medication both in the morning and in the evening at least 1 hour before meals. Placebo group received matching colored tablet twice daily.

3.4 Study Population
At the time of submission of this NDA, 531 patients were enrolled into this study. 262 patients were selected to receive trospium and 261 to receive the placebo.

3.4.1 Inclusion Criteria
Patients were entered in the study only if they met all of the following criteria:

1. Male and female patients, 18 years and older
2. Patients with Overactive Bladder (OAB) defined as:
   2.1 Urinary frequency of > 70 micturitions per week, as recorded in the patient diary
   2.2 Symptoms of urgency (i.e., sudden desire to micturite)
   2.3 Pure urge or mixed urinary incontinence with predominant urge incontinence.
   2.4 Patients must have at least seven urge incontinence episodes per week.
3. Symptoms of OAB for 6 or more months
4. Able and willing to correctly and independently complete the patient urinary diaries for 7 days and complete the quality of life questionnaire
5. Ability to use bathroom without assistance
6. Females of childbearing potential must have had a negative pregnancy test prior to enrollment. They should not be breast-feeding, and not at an appreciable risk of becoming pregnant.
7. Able to consent to participate by signing an informed consent form following an explanation of the nature and purpose of this study

Reviewer's Comment
Inclusion criteria for this study were adequate and acceptable

3.4.2 Exclusion Criteria
Patients were not entered in the study or were discontinued from the study for any of the following reasons:

1. History of total daily volume voided greater than 3000 ml collected in patient urinary diary
2. History of total average volume voided greater than 250 ml per void collected in patient urinary diary
3. Patients with stress incontinence, insensate incontinence (those incapable of distinguishing discrete incontinence episodes) and overflow incontinence, as major reason for urine loss or urinary frequency as determined by the investigator
4. Patients with history of neurogenic bladder
5. Patients with clinically significant renal disease
6. Patients with uninvestigated hematuria
7. Patients with acute urinary tract infections (UTI) during washout period and a negative urinalysis at screening visit, or recurrent UTI defined as receiving treatment for symptomatic UTI more than 2 times in the past year
8. Patients with clinically significant bladder neck obstruction defined as post-void residual urine greater than 100 ml
9. Patients with indwelling catheter or requiring intermittent catheterization
10. Patients with bladder surgeries performed within the past 6 months, or those who had surgeries leading to complications such as fistula
11. Females diagnosed with bladder cancer, interstitial cystitis within the past 6 months
12. Males with PSA > 10 Ng/ml or diagnosed with bladder cancer, prostate cancer, chronic prostatitis, or interstitial cystitis within the past 6 months
13. Patients treated within 21 days prior to randomization with any anticholinergic drug or other drug therapy for overactive bladder
14. Patients taking diuretics or estrogen therapy that was not part of a long-term stable program.
15. Patients employing bladder retraining / bladder drill programs
16. Patients who were anticipated to begin or change other bladder therapies (non-medicinal) such as biofeedback or kegels, during the course of the study
17. Patients with prior pelvic malignancies requiring radiation therapy or whose surgery had led to complications such as fistulas, etc
18. Patients with the history of any medical condition or taking concomitant medications that would have interfered with the patient's suitability and/or effective participation in the trial
19. Patients with the history of closed-angle glaucoma
20. Patients with the history of myasthenia gravis
21. Patients with hypersensitivity toward atropine, oxybutanin or adjuvants contained in the sugar-coated trospium chloride tablets
22. Females who were pregnant or breast feeding and if capable of bearing children, were not willing to use reliable contraception
23. Patients participating in another clinical trial or receiving a non-approved drug less than 30 days prior to screening

Reviewer's Comment
Exclusion criteria were adequate and acceptable

3.4.3 End Points

Co-Primary Efficacy Endpoint

1. **Change in the average number of toilet voids per 24 hours**
2. **Change in the average number of urge incontinence episodes per 24 hours**

"Total micturitions" as used in this study encompasses both "toilet voids" (non-incontinent micturitions) and incontinence episodes.

Secondary Endpoints

1. **Change in the average volume voided**
2. **Change in the average urgency severity**

Data to monitor both the primary and secondary efficacy endpoints was obtained from patient recorded urinary diary data. The data for toilet void frequency, number of incontinence episodes and frequency of urgency was recorded for seven full days prior to baseline, week 1, 4 and 12 visits. Data for average volume voided was collected for two full days prior to the clinic visit.

The measure used in the efficacy analysis was expressed as **change** (as computed by [Endpoint-Baseline]) and **percent change** (as computed by [Endpoint-baseline] / Baseline). The primary analysis was conducted using absolute change.

3.3.4 Patient Disposition

Table A.1 shows that a total of 523 patients were randomized into this pivotal study. 262 patients (59 M and 203 W) received the drug (trospium chloride) and 261 patients (75M and 186 W) received the placebo. The percent of patients who dropped out of the study were 86/523 (16.4%) i.e., 43 from each group. Adverse events (AE) were cited as the most common reason for the study discontinuation. Other reasons for drop-out were withdrawal of consent, non-compliance and lost to follow up.

Table A1: Patient Disposition

	Trospium	Placebo	Total
Number of Patients	**262**	**261**	**531**
Discontinued	**43**	**43**	**86 (16.4%)**
Adverse Events (AE)	**23 (8.8%)**	**15 (5.7%)**	**38 (7.3%)**
Withdrawal of Consent			**21**
Non-compliance			**6**
Lost to Follow-up			**15**
Other			**6**

3.4 Treatments

The identity of the study medication was blinded. The study medication was provided in the form of brownish-yellow, sugar coated tablets with no markings. The tablets either contained trospium chloride 20mg or a matching placebo tablet.

3.4.1 Patient Assignment to the Treatment Group

Each patient was assigned a screening number at the screening. Patients were randomized on 1:1 basis to receive either placebo or trospium chloride 20 mg twice daily during the study. Randomization for patients was stratified by the mean baseline number of micturitions (i.e., toilet voids and incontinence episodes per 24 hours collected via the patient diary over 7 days), using the stratified categories of 10 to 15, 16 to 20, and > 21 mean micturitions per 24 hours.

Randomized treatment assignment was accomplished with the use of an Interactive Voice Response System (IVRS). The IVRS performed the randomization using a two step process. The first step ensured that equal number of patients was assigned to each treatment group within the micturition stratification groups. The second step ensured that no site had >4 sequential assignments of the same study medication therapy. Once the randomization process was completed, the IVRS provided the study site.

Reviewer's comments

The main reason for randomizing subjects in the first place is the desirability of establishing treatment groups that are free of patient and physician selection bias.

Data suggests that the randomization worked well in this pivotal study. Trospium and placebo groups were comparable with regard to the factors that may affect patient response to the treatment.

3.4.2 Dosing, Labeling and Compliance

Each patient during this study was instructed by the investigator to take one tablet of study medication twice-daily one hour before meals. The study medication was packaged in 60 count, high-density polyethylene (HDPE) bottles with child-resistant closures and shipped to each site.

Each bottle was attached with a three part tear-off label. The label contained the following information: patient number, name/address of sponsor, investigational new drug statement, study number (IP 631-003), directions for use, storage instructions, and contents of the bottle with instructions to return the bottle and any unused medication.

Patients were instructed by the investigator of the study to bring their bottles containing unused study medication with them for a compliance assessment at Day 8, Day 28, and Day 84 study visits. Compliance was assessed by unused tablet counts and details recorded in eCRF.

4.0 Efficacy Results

The sponsor conducted the review of efficacy in three phases: Screening, baseline and double blind treatment phases.

During the **screening visit** i.e., Day (-) 21 for patients, who were already on OAB medication and Day (-) 8 for patients, who were not currently taking OAB medication, screening assessments were made for patient's eligibility for the study.

Baseline phase from Day (-) 8 to Day 0, was the time when the indicated baseline assessments were made, including assessment of week 1 of patient urinary diary data prior to the first dose of study medication.

Treatment phase included Day 1 to Day 84 (week 12). During this time, patients either received the placebo or trospium chloride 20-mg tablet twice daily. Dosing according to the sponsor was begun on Day 1 following the baseline visit (Day 0). Assessments of both efficacy and safety were performed during this phase of the study.

As demonstrated by the following results, this well controlled pivotal study (IP 631-003) provides substantial evidence in support of the effectiveness of trospium chloride 20mg bid for reduction in overactive bladder symptoms (i.e., toilet voids, incontinence episodes, and volume voided) over a 12 week period.

The primary efficacy variables in this study were based on data collected over 7 days prior to the baseline, Day 8 (week 1), Day 28 (week 4), and Day 84 (week 12) visits, using data recorded in patient urinary diaries. Considering each variable separately for each patient, an "Analysis week" was only used for analysis if the entries were made for at least 4 full days of the 7 required days. If only 4, 5, or 6 days of data entries were available to the investigator, they were normalized to 7 days.

The key efficacy analyses focussed on the change from baseline to Day 84 (week 12) visits.

Sponsor conducted all primary and secondary efficacy assessments using intent to treat (ITT) patient sample. The ITT sample included all patients who were enrolled (i.e., randomized and dispensed study medication) and had at least one post-baseline evaluation.

Efficacy analyses were done using the last observation carried forward (LOCF) data set, which consisted of data recorded or carried forward at each visit.

Sponsor conducted the supportive analyses for primary efficacy variables using the observed cases (OC) data set. The OC data set consisted of only the actual data recorded at each visit.

4.0.1 Primary Efficacy Results
Sponsor's objective for this study was to determine the effects of 20 mg of trospium versus placebo, given twice daily in patients with overactive bladder associated with urge incontinence over a 12-week treatment period. The co-primary efficacy variable change as seen during the study were as follows:

4.1.1 Change in the average number of toilet voids per 24 hours: There was a decrease (an improvement) in the number of toilet voids per 24 hours at week 1 with trospium chloride which was statistically significantly different from placebo ($p=0.05$). At week 4 and 12, there was a further decrease in average number of toilet voids, which was determined to be statistically significant ($p<0.001$) (See table A.2)

4.1.2 Change in the average number of incontinence episodes per 24 hours:
At weeks 4 and 12 trospium showed a decrease in the average number of urge incontinence episodes per 24 hours as compared to the placebo group and the findings were statistically significant ($p< 0.05$). (See table A.2)

4.2 Secondary Efficacy Results

4.2.1 Change in the average volume voided (ml) per toilet void: Trospium chloride demonstrated an increase in the volume voided per toilet void at weeks 1, 4, and 12 when compared to the placebo group ($p<0.001$). (See table A.2)

4.2.2 Change in average urgency severity associated with toilet voids:
Trospium demonstrated an improvement (a decrease) in the urgency severity in non-incontinent toilet voids at weeks 1, 4, 12 when compared to the placebo group, which was statistically significant ($p<0.05$). (See table A.2). It remains unclear whether this 4-point scale is adequately validated.

4.3 Effect Across Outcomes
Sponsor points out that trospium chloride demonstrated a change (a decrease) in average number of total micturitions (i.e., toilet voids and urge incontinence episodes) per 24 hours at weeks 1, 4, and 12 when compared to the placebo, which was statistically significant.

These efficacy endpoint changes were recorded in the patient urinary diary by the patient at each voluntary and /or incontinent event. If a patient experienced urinary incontinence and was then able to get to the toilet to complete the void, the patient was instructed to record this event in the urinary diary as both an episode of urinary incontinence and a

toilet void. The diary was reviewed by the investigator at each scheduled visit and then entered into the eCRF. Patients were asked to keep a 7-day patient diary record prior to study start to ensure understanding and compliance and for use as baseline data in the statistical analyses.

Only complete data for full 24-hour days (from the diaries) was included in the calculation of each variable. Entries were made in the patient urinary diaries for 7 full days prior to study (during baseline period), as well as 7 full days prior to each study visit. The analysis week was not used for analysis if entries were not made for at least 4 full days of the 7 required days. If only 4, 5 or 6 full days of entries were available, they were normalized to 7 days. Volume voided was collected for 2 full days prior to each study visit.

An exploratory analysis of treatment onset of action for effect on toilet voids, urge incontinence episodes and total micturitions per 24 hours were evaluated using comparisons of days within week 1.

4.4 Onset of Action

In an exploratory analysis, onset of action during week 1 for effect on toilet voids, urge incontinence episodes and total micturitions per 24 hours trended toward a treatment effect starting on Day 3 and was statistically significant for trospium group compared to placebo group beginning at Day 7 and continuing through Day 11.

4.5 Other Efficacy Endpoints

Quality of life data

In addition to examining efficacy variables collected from patient urinary diaries, quality of life and symptom annoyance was assessed in female patients using the incontinence impact questionnaire (IIQ). The IIQ is a 30-item self-reported, validated scale designed to assess the impact of urinary incontinence on 4 sub-scales. The sub-scales included travel, physical activity, social relationships and emotional health. A modified incontinence impact questionnaire of 20 self- reported items was used in male patients.
Analyses were done on subsets of the gender-specific questionnaires and on combined data sets, which has not been submitted as yet.

Reviewer's Comment

The quality of life measurements support the primary and key secondary efficacy endpoints. The questionnaire needs to be submitted by the sponsor for our assesment of adequacy of its validation.

4.6 Efficacy Conclusions

Trospium demonstrated statistically significant improvement for both of the co-primary efficacy variables and for key secondary efficacy variables when compared with placebo. A summary of results for the efficacy endpoints is summarized in the table below:

Table A2. Summary of Results for Efficacy Endpoints
Mean Change from Baseline

Efficacy Endpoint	Week	Trospium	Placebo	p-value
Number of toilet voids per 24 hours		N=253	N=256	
Change from baseline	1	-1.18	-0.81	.0509
	4	-2.20	-1.07	<0.0001
	12	-2.37	-1.29	<0.0001
Number of urge incontinence episodes per 24 hours		N=253	N=256	
Change from baseline	1	-1.40	-1.35	0.1195
	4	-2.02	-1.87	0.0025
	12	-2.20	-1.98	0.0118
Volume voided (ml) per toilet void per 24 hours		N=248	N=253	
Change from baseline	1	19.88	6.55	<0.0001
	4	29.96	8.45	<0.0001
	12	32.14	7.72	<0.0001
Urgency severity associated with toilet voids		N=253	N=256	
Change from baseline	1	-0.11	-0.01	0.0033
	4	-0.18	-0.06	0.0041
	12	-0.22	-0.04	0.0001

4.6.1 Primary Efficacy Conclusions

Trospium demonstrated statistically significant ($p<0.05$) improvement (i.e., decrease) for the primary efficacy variables of change in average number of toilet voids per 24 hours (at weeks 4, and 12) and change in average number of urge incontinence episodes per 24 hours (at weeks 4 and 12) when compared with the placebo group.

Trospium demonstrated a statistically significant ($p<0.001$) improvement (i.e., decrease) in average number of urge incontinence episodes per week at both weeks 4 and 12 when compared with the placebo group. Sponsor points out that the results from a descriptive analysis using univariate procedure showed that 71% of patients treated with trospium had a 50% reduction in the number of incontinence episodes per 24 hours whereas, only 54% of placebo treated patients had the same effect. Similarly, 21% of the trospium treated patients had their number of incontinence episodes reduced to zero (0) per 24 hours while only 11% placebo treated patients achieved this endpoint. Therefore, in thi

exploratory analysis, trospium was able to "eliminate" incontinence episodes in twice as many patients as did placebo.

As reported by the sponsor, trospium demonstrated statistically significant improvement i.e., (decrease in average number of diurnal toilet voids) at weeks 1,4, and 12 weeks and also a decrease in average number of nocturnal toilet voids at weeks 4 and 12 when compared to placebo. The assessment of trospium effect on nocturnal voids was also an exploratory analysis.

Reviewer's Comment

It is the opinion of this reviewer that the patients treated with trospium chloride, in this pivotal study, not only had a decrease in the number of toilet voids per 24 hours and most had a 50% reduction in the number of incontinence episodes per 24 hours, but also experienced a clinically meaningful improvement in their symptoms and a suggested improvement in quality of life. The magnitude of the treatment effect was consistent across different age groups, geographic locations and baseline incontinence severity.

4.6.2 Secondary Efficacy

Sponsor reports that trospium demonstrated statistically significant improvement (increase) in average volume voided at weeks 1,4, and 12 when compared to the placebo.

Trospium has also showed statistically significant improvement (i.e., decrease) in the average urgency severity 4-point scale at weeks 1,4, and 12 when compared to the placebo. The validation of the scale is still under evaluation.

Reviewer's Comment

This reviewer concludes that the evidence from this well controlled study supports the effectiveness of trospium chloride (20 mg bid) for the treatment of overactive bladder as is evident from the change seen in both co-primary and key secondary end points. The overall risks/benefit ration will be addressed in a different section.

5.0 Safety Results

5.1 Brief Statement of Safety Conclusions

The adverse event profile of trospium chloride appears to be similar to that of other anti-cholinergic drugs. Dry mouth, abdominal cramps, constipation and headache were the most frequently reported events over a 12-week treatment period.

Other less frequently reported but clinically important adverse events included chest pain and urinary retention. None of these resulted in a serious adverse event.

No hepatotoxicity was seen. However, there was a mild increase in serum transaminases in some individuals in this trial, not seen in other trials.

There was also no evidence of any syncope among the patients with overactive bladder on trospium treatment.

No apparent QT safety signal has been identified among patients in this study nor in the thorough QT study (**IP631-010**) using a positive control and both recommended and high dose trospium. The study results were submitted in Feb. 2004 and showed no signal of any effect of clinical dose of 20-mg and 100-mg bid on cardiac repolarization or conduction. However, there was evidence of t-wave inversion superimposed on tachycardia seen in clinically asymptomatic patients.

5.2 Description of Patient Exposure

As of November 2003, the sponsor has completed study (IP631-003) at 51 US clinical sites. 531 patients with overactive bladder, who met the inclusion criteria, were enrolled into the study. There were a total of 523 patients. 262 received trospium chloride 20 mg twice daily and 261 patients received the placebo for treatment duration of 12 weeks.

Data from adverse events, clinical laboratory test results, vital signs, ECG and deaths were reviewed to evaluate the safety and tolerability of trospium.

5.3 Adverse Events

Sponsor reports that there were 61 patients [trospium 35 patients (13.4%), placebo 26 patients (10.0%)], who experienced one or more adverse events during the baseline phase, but no patient was reported to have experienced a serious adverse event during the baseline phase.

5.4 Treatment Emergent Adverse Events (TEAE's)

At least one TEAE was reported in a total of 309 patients (trospium 171 [65.3%] patients, placebo 138 [52.9%] patients). TEAE's were most commonly reported for the gastrointestinal system; as reported by 92 patients (35.1%) in the trospium group and 62 patients (23.8%) in the placebo group.

Table A3. All TEAEs in Study IP631-003 summarized by severity

	Number of patients (%)	
	Placebo	Trospium
TEAE severity	N=261	N=262
Total patients with at least one TEAE	**138 (52.9)**	**171 (65.3)**
Mild	60 (23.0)	93 (35.5)
Moderate	70 (26.8)	64 (24.4)
Severe	8 (3.1)	14 (5.3)

The most common trospium related TEAE's were dry mouth, constipation, abdominal pains, headache, chest pain and urinary retention.

Table A4. Incidence of all TEAEs in Study IP631-003 in Placebo and Trospium Groups (all causality)

	Number of patients (%)	
	Placebo	Trospium
Preferred term	N=261	N=262
Total patients with at least one TEAE	138 (52.9)	171 (65.3)
Dry mouth	17 (6.5)	57 (21.8)
Constipation	10 (3.8)	25 (9.5)
Headache NOS	12 (4.6)	17 (6.5)
Abdominal pain NOS	3 (1.1)	8 (3.1)
Diarrhea NOS	14 (5.4)	8 (3.1)
Abdominal pain upper	7 (2.7)	7 (2.7)
Dyspepsia	6 (2.3)	7 (2.7)
Fatigue	3 (1.1)	7 (2.7)
Flatulence	5 (1.9)	6 (2.3)
Chest pain	1 (0.4)	6 (2.3)
Urinary tract infection NOS	7 (2.7)	6 (2.3)
Dizziness	2 (0.8)	6 (2.3)
Urinary retention	1 (0.4)	6 (2.3)
Nausea	7 (2.7)	5 (1.9)
Upper respiratory tract infection NOS	6 (2.3)	5 (1.9)
Cough	10 (3.8)	5 (1.9)
Pyrexia	8 (3.1)	1 (0.4)
Pharyngolaryngeal pain	7 (2.7)	1 (0.4)
Rash NOS	10 (3.8)	1 (0.4)

Table A5. Most Common TEAE's in Study IP631.003 in both Treatment Groups (all-causality)

	Placebo N=261	Trospium N=262
Patients with at least one TEAE	138(52.9%)	171(65.3%)
Dry Mouth	17(6.5%)	57(21.8%)
Constipation	10(3.8%)	25(9.5%)
Headache	12(4.6%)	17(6.5%)
Abdominal Pain	3(1.1%)	8(3.1%)
Chest Pain	1(0.4%)	6(2.3%)
Urinary Retention	1(0.4%)	6(2.3%)

From the most common TEAE's presented in the two tables above, it is seen that dry mouth and constipation occurred in > 5.0% of trospium patients ($p<0.01$) which seems to be consistent with the anticholinergic effect of trospium chloride.

However, there are two other significant TEAE's i.e., chest pain and urinary retention seen during this trial.

5.4.1 Chest pain

There were a total of 7 patients who experienced chest pain during this trial [trospium 6 patients (2.3%) and placebo 1 patient (0.4%)]. Of the 6 patients on trospium who developed chest pain, 1 patient experienced severe chest pain, 2 patients experienced chest pain and had to be hospitalized, and 1 patient experienced chest pain that led to discontinuation of study medication.

For 4 out of 6 patients on trospium who experienced chest pain, sponsor believes that there was no relationship to the study drug. The remaining two patients on trospium who experienced chest pain had prior co-morbidity's i.e., cardiovascular disease but no active ischemia. The relationship to the study drug in these two cases could not be ruled out for either a probable or possible relationship.

Reviewer's comment

This reviewer agrees with the assessment in this submission that none of the six patients on trospium experienced chest pain related to active myocardial ischemia. These reports appearred to be consistent with non-cardiac chest pain.

Narratives of Patients with Chest Pain

Patient # 15-6124

69 year old white male with past medical history significant for HTN, systolic ejection murmur, shortness of breath, GERD, hyper-cholestrolemia, BPH and obesity, who was enrolled in study IP631-003, after receiving his first dose of trospium chloride experienced chest discomfort. The patient attributed this to smoke from a forest fire near to his home. The discomfort was mild and resolved without sequelae. Study medication was discontinued. The condition was determined by the investigator as **remotely related** to the study drug.

Patient # 34-6052

69 year old white female with significant past medical history of mitral valve prolapse, spastic colon, arthritis, hystrectomy, s/p bilateral hernial repair was enrolled in study IP631-003, experienced chest pain and tachycardia 17 days after the study drug administration, which was moderate in intensity. The study medication was temporarily interrupted for 48 hours. The patient was ruled out for any active ischemia and the chest pain resolved without any sequelae. Relation to the study drug was thought to be **probably related** by the investigator.

Patient # 36-6215
36 year old African-American female with significant past medical history of asthma and benign lymph-adenopathy, who was enrolled in study IP631-003 experienced mild chest pain, 11 days after the first dose of trospium chloride. Patient was ruled out for any active ischemia. The relation was determined to be **definitely not related** to the study medication. In fact, it was determined attributed to excessive caffeine consumption by the patient.

Patient #44-6358
48 year old white female with significant past medical history of anemia, anxiety, depression, macular degeneration, urethral stenosis, fibroid disease, herniated cervical disc and arthritis who was enrolled in study IP631-003 and experienced atypical chest pain 30 days after receiving the first dose of trospium chloride. The patient was ruled out for active ischemia. The condition resolved without any sequelea. The study drug, which had been briefly interrupted, was resumed back and the relation to study drug was determined to be **definitely not related** by the investigator.

Patient # 47-6418
63 year old white male with significant past medical history of obesity, ED, arthritis, smoking and hypertensive urgency who was enrolled in study IP631-003 experienced two episodes of chest pain 37 days after the first dose of trospium chloride. The pain itself resolved with rest. Patient was admitted to hospital and discharged 24 hours later. He ruled out for active ischemia or MI. The investigator determined it to be **definitely not related** to the study medication.

Patient # 52-6532
57 year old white female with significant past medical history of hystrectomy, disc pain, arthritis, pancreatitis and depression who was enrolled in study IP631-003 experienced chest pain 26 days after first dose of trospium chloride. The cardiac work up was negative but the chest pain continued off and on. However, the patient decided to withdraw from the study

Patient # 24-6525
64 year old white male with significant pat medical history of BPH, COPD, GERD, smoker, and use of alcohol was enrolled in study IP631-003, who experienced chest pain 34 days after administration of first dose of placebo. Patient concurrently also had symptoms of airway obstruction. Patient was ruled out for any active cardiac ischemia and was treated for airway obstruction. Study medication was not interrupted and the relation to the study medication was determined to be **remotely related** by the investigator.

5.4.2 Urinary Retention
A total of 7 patients [trospium 6 patients (2.3%) and placebo 1 patient (0.4%)] experienced urinary retention during this trial. According to the sponsor, none of these

urinary retention events were severe or serious, but in 4 out of 6 patients who experienced urinary retention among the trospium group, the study medication had to be discontinued.

The sponsor believes that 5 out of 6 patients who experienced urinary retention while on trospium chloride were possibly related to the study medication.

Reviewer's Comment

This reviewer agrees with the assessment in this submission that 5 out of 6 patients on the study medication experienced urinary retention/post void fullness that was possibly/probably a result of trospium. However, it is notable that all of them had pre-existing multiple medical illnesses possibly contributing to urinary retention. Also 47% of patients on trospium, who developed urinary retention had outlet obstruction due to pre-existing BPH.

Additional Comments

1. Like other anticholinergic drugs, trospium chloride appears to have GI side effects. The analysis of severity and frequency is summarized in the Table on page 16.

2. Despite the notable incidence rates of GI events, this reviewer has no major concerns regarding the events listed as dry mouth, constipation, abdominal pain and headache. While they can be bothersome to the patient, these events rarely lead to significant clinical consequences and resolve when the drug is discontinued. It is therefore reasonable to expect that the majority of patients and prescribers would be able to recognize these events and stop taking medication if and when necessary.

5.5 Serious Treatment Emergent Adverse Events

Sponsor in this submission reports 15 patients [trospium 9 patients (3.4%) and placebo 6 patients (2.3%)] that experienced serious TEAE as shown in the table below.

Table A6. Serious TEAE's

	Number of patients (%)	
Criterion for serious TEAE	Placebo N=261	Trospium N=262
Total patients with at least one TEAE	**138 (52.9)**	**171 (65.3)**
Total patients with at least one serious TEAE	**6 (2.3)**	**9 (3.4)**
Death	0 (0.0)	1 (0.4)
Life-threatening	1 (0.4)	0 (0.0)
Hospitalization required or prolonged	5 (1.9)	9 (3.4)
Required medical intervention	2 (0.8)	0 (0.0)

The sponsor believes that the most serious TEAE's reported during this were not life-threatening except for one in the trospium group, which resulted in death. All these serious events as assessed by the investigator were remotely related to the study medication.

The study medication was permanently discontinued in 2 out of 9 patients in the trospium group (i.e., patient with ovarian cancer and hemorragic stroke). Study medication was temporarily interrupted in two patients (i.e., patient with gastroenteritis and patient with chest pain). One patient in the trospium group, who experienced a hemorrhagic stroke, resulted in death. In the remaining patients, the serious TEAE's resolved with no change in study medication.

In the placebo group all TEAE's resolved with the exception of patient who developed breast cancer. The events of cholelithiasis and coronary artery disease (as shown in the table below) both occurring in the placebo group required medical intervention. Other patient in placebo group who experienced a myocardial infarction with subsequent sustained unstable ventricular tachycardia was life threatening.

Table A7. Patients in Study IP631-003 with at least one serious TEAE

	Number of patients (%)	
	Placebo	Trospium
Preferred term	N=261	N=262
Total patients with at least one TEAE	**138 (52.9)**	**171 (65.3)**
Total patients with at least one serious TEAE	**6 (2.3)**	**9 (3.4)**
Chest pain [a]	1 (0.4)	2 (0.8)
Asthma aggravated	0 (0.0)	1 (0.4)
Esophagitis NOS	0 (0.0)	1 (0.4)
Gastroenteritis NOS	0 (0.0)	1 (0.4)
Hemorrhagic stroke	0 (0.0)	1 (0.4)
Major depressive disorder NOS	0 (0.0)	1 (0.4)
Ovarian cancer NOS [b]	0 (0.0)	1 (0.5)
Subdural hematoma	0 (0.0)	1 (0.4)
Breast cancer NOS [b]	1 (0.5)	0 (0.0)
Cholecystitis acute NOS	1 (0.4)	0 (0.0)
Cholelithiasis	1 (0.4)	0 (0.0)
Coronary heart disease NOS	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Sinoatrial node dysfunction	1 (0.4)	0 (0.0)
Ventricular tachycardia	1 (0.4)	0 (0.0)