In the two, randomized, placebo-controlled, healthy adult volunteer studies, Mirabegron was associated with dose-related increases in standardized urinary frequency. Mean standardized urinary frequency increased from a median of 0.27 episodes per 2.5-hour period in placebo treated volunteers to 0.53 and 0.70 episodes per 2.5-hour period in volunteers treated with 50 mg Mirabegron daily and 100 mg Mirabegron daily, respectively. Mirabegron treatment did not significantly affect the median time to the first void in either study.

No new safety issues were detected with Mirabegron treatment in these studies.

b) Safety in patients with detrusor overactivity with or without urge incontinence

In the study to evaluate the effects of Mirabegron 25 mg and 50 mg administered once daily for 14 days to 20 patients with detrusor overactivity with or without urge incontinence, mean standardized urinary frequency increased from a median of 0.13 episodes per 2.5-hour period in placebo treated volunteers to 0.26 and 0.37 episodes per 2.5-hour period in volunteers treated with 25 mg Mirabegron daily and 50 mg Mirabegron daily, respectively. Patients treated with Mirabegron also demonstrated a significant increase in mean daily voided volume and a significant decrease in mean nocturnal wetting compared to placebo treated patients. There were no significant changes in other endpoints such as mean bladder weight, mean bladder capacity, or mean number of nighttime voids. Mirabegron also did not significantly affect the incidence of nocturnal urgency, nocturnal enuresis, or day time urgency compared to placebo treated patients. In addition, Mirabegron treatment did not significantly affect the median time to the first void in either study.

No new safety issues were detected with Mirabegron treatment in these studies.

In the 12-week, randomized, parallel-group, placebo-controlled study, a total of 1065 patients with urge incontinence (mean age 64 years, 72% female) were randomized to receive placebo, Mirabegron 25 mg, or Mirabegron 50 mg once daily. The primary efficacy endpoint was a 50% or greater reduction in daily incontinence episodes from baseline to week 12.

Mirabegron was associated with statistically significant reductions in daily incontinence episodes at Week 12 compared to placebo in a dose-dependent manner. Mean reductions in daily incontinence episodes at Week 12 were approximately 20% for patients treated with placebo, 40% for those treated with Mirabegron 25 mg once daily, and 50% for those treated with Mirabegron 50 mg once daily. Mean reductions in daily incontinence episodes were maintained throughout the study in both the 25 mg and 50 mg treatment groups. The majority of patients (>70%) who had a response of 50% or greater at week 12 had sustained improvement throughout the study.

In the 12-week, placebo-controlled study, patients were randomized to receive placebo, Mirabegron 25 mg, or Mirabegron 50 mg once daily. The primary efficacy endpoint was a 50% or greater reduction in daily incontinence episodes from baseline to week 12. In addition, patients had a mean age of 64 years, 72% female. The primary outcome measure was the percentage of patients with >50% reduction in daily incontinence episodes from baseline to Week 12.

Mirabegron was associated with statistically significant reductions in daily incontinence episodes at Week 12 compared to placebo in a dose-dependent manner. Mean reductions in daily incontinence episodes at Week 12 were approximately 20% for patients treated with placebo, 40% for those treated with Mirabegron 25 mg once daily, and 50% for those treated with Mirabegron 50 mg once daily. Mean reductions in daily incontinence episodes were maintained throughout the study in both the 25 mg and 50 mg treatment groups. The majority of patients (>70%) who had a response of 50% or greater at week 12 had sustained improvement throughout the study.

There were no new safety issues detected in these studies.
**Geriatric**

The pharmacokinetics of mirabegron were studied in elderly subjects. Approximately 10% of the elderly population in the US are at risk and only a small number of healthy volunteers in the study population met criteria for geriatric patient characteristics.

Specific Populations

- **Elderly:** elderly patients (aged 65 years or older) were similar to those younger than 65 years in terms of 
- CYP2D6, CYP3A4, and P-glycoprotein expression and activity.
- **Renal Impairment:** the renal impairment population included mild (creatinine clearance [CrCl] 50 to 80 mL/min] or moderate [CrCl 30 to 50 mL/min] renal impairment.
- **Hepatic Impairment:** the hepatic impairment population included mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

- **Co-administration Studies:** the pharmacokinetics of mirabegron were studied in combination with rifampicin, ketoconazole, and clarithromycin.

- **CYP2D6:** Cohen et al have reported that the exposure to the racemic form of mirabegron was increased by 25% in CYP2D6 poor (PM) individuals compared to the normalizer group. In each of the three dose groups of the study, the exposure to the S-enantiomer and the R-enantiomer was increased by 25% and 22%, respectively.

- **CYP3A4:** mirabegron is a substrates of CYP3A4 and P-glycoprotein. In the presence of co-administered drugs with CYP3A4 or P-glycoprotein inhibition, the exposure to both the S-enantiomer and the R-enantiomer of mirabegron was reduced by 65% and 66%, respectively.

- **P-glycoprotein:** the exposure to both the S-enantiomer and the R-enantiomer of mirabegron was increased by 33% and 49%, respectively.

- **Clinical studies:** the pharmacokinetics of mirabegron were studied in combination with warfarin, digoxin, and tamsulosin.

- **Warfarin:** the exposure to warfarin was increased by 6.0% when co-administered with mirabegron.

- **Digoxin:** the exposure to digoxin was increased by 6.8% when co-administered with mirabegron.

- **Tamsulosin:** the exposure to tamsulosin was decreased by 25% when co-administered with mirabegron.

The magnitude of these interactions of the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

- **Clarithromycin:** moderate P-glycoprotein inhibition (clarithromycin 500 mg qd) increased the AUC of the S-enantiomer and the R-enantiomer by 15% and 9%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

- **Clarithromycin:** moderate P-glycoprotein inhibition (clarithromycin 500 mg qd) increased the AUC of the S-enantiomer and the R-enantiomer by 15% and 9%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.

The magnitude of these interactions suggests that the pharmacokinetics and the recommendations for dose adjustments for these drugs are as follows:

- **Rifampicin:** moderate CYP3A4 inhibition (rifampicin 600 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 84% and 76%, respectively.

- **Ketoconazole:** moderate CYP3A4 inhibition (ketoconazole 400 mg qd) decreased the AUC of the S-enantiomer and the R-enantiomer by 42% and 53%, respectively.