screening (Visit 1, patient's reflective TSS for the previous 12 hours had to be ≥ 6 (excluding nasal congestion and ≥ 2 additional SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe' on a 0-4 scale [0=none, 1=mild, 2=moderate, 3=severe, 4=very severe], and no symptom was to be rated 'very severe') and the baseline visit (Visit 2, these patients were required to have a 7:00 p.m. reflective TSS ≥ 5 with 2 or more symptoms (excluding nasal congestion) with a score of "2". Like the adult SAR trials, the TSS could range from 0-16. Unlike the adult SAR trials, however, the pediatric trials evaluated bid dosing of fexofenadine at distinctly lower doses (15 mg, 30 mg, and 60 mg bid). Rescue medication use was not allowed in either of these 2 trials.

The primary efficacy endpoint in these 2 studies was defined as the change from baseline in the average 7:00 p.m. reflective TSS over the 2 week double-blind treatment period (note patients took their 1st dose of study medication at 7:00 p.m.). Because of its importance in ascertaining maintenance of drug effect, the medical reviewer also added the change from baseline in average daily 7:00 a.m. and 7:00 p.m. instantaneous TSS over the 2-week double-blind treatment period, as measures of the end-of-dosing interval.

An important study design issue for the pediatric SAR trials was the combination of studies 0066 and 0077 into a single combined trial-0066/0077 because of 'lower-than-anticipated' enrollment into each study alone [V1.63:223]. When both of these studies were combined, lack of a statistically significant effect of the fexofenadine treatments compared to placebo was seen for the primary and most of the secondary efficacy endpoints. Hence, each individual SAR study is presented independently, with the finding of statistically significant improvement in SAR symptoms in study 0077 but not 0066. While a number of different rationales were explored by the sponsor to explain this discrepancy (including differences in pollen counts, compliance with medications, protocol violations, baseline symptom severity, age, outliers, or possibility of a drug packaging error) no plausible explanation for this difference was found by the sponsor. Nonetheless, the high placebo response evident in study 0066 may explain lack of statistical significance in this study, which would have also impacted on the integrated efficacy of combined studies 0066/0077. Importantly, for all efficacy endpoints evaluated, numerical trends for study 0066 (and likewise combined study 0066/0077) indicate improvement in symptom scores in fexofenadine treated patients. The statistical reviewer and the Division of Biometrics II concluded after review of the combined pediatric study and individual studies that studies 0066 and 0077 are not poolable due to a statistically significant 0.05 level study-by-treatment interaction term (p=0.0432) [NDA 20-872, Statistical Review, Barbara Elashoff, p.18].

Across the 3 fexofenadine doses, a dose response was not seen. Subgroup analysis of the primary efficacy variable failed to show any influence of demographic factors on treatment effect but did reveal a statistically significant baseline-by-treatment interaction at the 0.1 level (p=0.0629), indicating that

treatment effect varied with baseline symptom severity (i.e. a larger reduction in symptom scores noted in more symptomatic patients) [V1.225:97].

Results of the pediatric SAR efficacy data for the 3 endpoints discussed above is presented in Table VII. below.

Table VII. Summary of Primary Efficacy Data for Pediatric SAR Studies: 0066/0077 combined and individual studies 0066 and 0077 [V1.225:75-78, V1.297:12-15]

	TREATMENT GROUPS				P-value:		
	Fexo 15 mg bid	Fexo 30 mg bid	Fexo 60 mg bid	Placebo	Fexo 15 mg bid c/w placebo	Fexo 30 mg bid c/w placebo	Fexo 60 mg bid c/w placebo
Change from baseline in the average 7:00 p.m. reflective TSS (Mean Difference ± [1]SE, % Δ from baseline) (Designated the a priori primary efficacy endpoint)							
Pediatric combined SAR studies 0066/0077	-1.49 ± .163 (-19.3%)	-1.54 ± .169 (-19.8%)	-1.55 ± .167 (-20.1%)	-1.21 ± .161 (-15.0%)	0.2197	0.1585	0.2227
Study 0066	-1.30 ± .248 (-16.5%)	-1.53 ± .258 (-19.2%)	-1.44 ± .256 (-18.6%)	-1.59 ± .236 (-19.4%)	0.3559	0.8470	0.6442
Study 0077	-1.83 ± .246 (-24.4%)	-1.65 ± .253 (-21.8%)	-1.73 ± .277 (-22.6%)	-0.84 ± .241 (-10.7%)	**0.0023**	**0.0138**	**0.0318**
Change from baseline in average daily 7:00 a.m. instantaneous TSS							
Pediatric combined SAR studies 0066/0077	-0.98 ± .153 (-13.7%)	-0.89 ± .160 (-13.0%)	-0.91 ± .158 (-13.3%)	-0.66 ± .151 (-9.3%)	0.1213	0.2919	0.2479
Study 0066	-0.87 ± .241 (-12.2%)	-0.83 ± .251 (-11.7%)	-0.81 ± .250 (-11.6%)	-0.97 ± .229 (-13.3%)	0.7473	0.6574	0.5991
Study 0077	-1.22 ± .223 (-19.2%)	-1.00 ± .233 (-15.3%)	-1.05 ± .229 (-15.8%)	-0.29 ± .219 (-4.2%)	**0.0018**	**0.0175**	**0.0104**
Change from baseline in average daily 7:00 p.m. instantaneous TSS							
Pediatric combined SAR studies 0066/0077	-0.94 ± .162 (-14.3%)	-1.06 ± .170 (-16.1%)	-1.02 ± .167 (-15.2%)	-0.70 ± .160 (-10.0%)	0.2935	0.1156	0.1625
Study 0066	-0.79 ± .278 (-11.4%)	-1.13 ± .261 (-16.1%)	-0.79 ± .261 (-11.8%)	-0.93 ± .238 (-13.2%)	0.6391	0.5468	0.6598
Study 0077	-1.17 ± .243 (-19.2%)	-1.04 ± .253 (-17.0%)	-1.21 ± .249 (-19.8%)	-0.40 ± .239 (-5.8%)	**0.0168**	**0.0484**	**0.0116**

[1]SE=Standard Error. P-values, means and associated std errors from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity.

These data indicate that for both the 12-hour reflective total symptom scores and the end-of-dosing interval, all fexofenadine treated patients in study 0077 demonstrated a statistically significantly greater decrease in symptom scores than placebo. Based on numerical values and the degree of change in symptom scores across studies (including the combined studies), the most appropriate fexofenadine dose numerically would appear to be the 15 mg bid dose, although no consistent dose response (from 15 mg to 60 mg) was demonstrable (especially

in the "successful" study 0077), however based on pediatric PK data, the 30 mg dose afforded plasma fexofenadine levels that were most comparable to the 60 mg dose in adults (linkage of pediatric and adult PK via the Pediatric Rule). The numerical differences between active treatments were overall small and the dose response, when seen for a particular clinical endpoint, could hence be described at best, as shallow. Review of secondary efficacy endpoints supported findings seen in the primary efficacy variable, namely statistical significance was achieved for almost all endpoints in study 0077, but in almost none for study 0066 and 0066/0077 combined [V1.225:82-93, 297:6-17]. Evaluation of the week 1 vs. week 2 response for the primary efficacy endpoint for the combined and separate studies overall revealed a numerically greater decrease in TSS by week 2 of treatment, but one which was only statistically significant for study 0077 [V1.225:84-85, V1.297:6-9].

Subgroup analysis by race, gender, weight, study site, and baseline symptom severity revealed a statistically significant treatment interaction for baseline symptoms (p=0.0629) [V1.225:97], indicating that treatment effect varied with the level of baseline symptoms (i.e. a larger treatment effect for more symptomatic patients). For the other 4 variables, no treatment interaction effect was seen.

9.4. Summary of the Primary Efficacy Data (including the end-of dosing interval) for the Adult CIU Studies

The 3 adult CIU studies were very similar in study design, with some greater differences noted in study 0019. While fexofenadine tablets were utilized in studies 0039 (pivotal trial) and 0067, capsules were utilized in study 0019. Studies 0039 and 0067 evaluated patients 12-65 years of age, whereas study 0019 evaluated patients ≥ 18 years of age. All 3 studies were characterized by a lead-in period (24-hour single-blind for studies 0039 and 0067, and a 14 day unblinded lead-in period for study 0019). Patients received from 4-6 weeks of double-blind study medication (again, duration varied with CIU study). Like the SAR trials, enrollable patients were required to have a pre-determined level of baseline symptom severity in order to participate in the study (for studies 0039 and 0067 these criteria were defined as: ≥ 1 wheal at the time of randomization (or score ≥ 1), and at least moderate severity of patient self-rated pruritus (score ≥ 2), for a total symptom score (TSS): a composite score of the number of wheals (0-4 scale) and the pruritus scale (scale 0-4) ≥ 3), for study 0019 this criteria consisted of: a rating of urticarial lesions as at least 'moderate' or 'severe' on at least 1 occasion in the preceding 2 weeks). Like the SAR trials, patients rated their symptoms twice daily in a diary. Rescue medication use was not allowed in studies 0039 and 0067, but in study 0019 H_2 antagonist use was allowed as rescue medication for the study duration.

The primary efficacy endpoint for studies 0039 and 0067 was defined as the: change from baseline in the mean 'reflective' pruritus score (MPS, maximum

score of 4), whereas the primary efficacy endpoint for study 0019 was defined as the: change from baseline in the mean daily reflective total symptom score (TSS=composite score of the mean pruritus score (0-3 rating scale) and the # of wheals score (0-4 rating scale; for a total maximal score of 7). The end-of-dosing interval was not assessed in any of the 3 CIU studies. Results of the primary efficacy analysis are presented in Tables VIII. and IX. below, with separation of studies based on dosing regimen (bid vs. qd):

Table VIII. Summary of CIU Studies (0039, 0067) that Evaluated Twice Daily (bid) Dosing of Fexofenadine [V1.170:79, V1.178:12, V1.189:79]

	TREATMENT GROUPS					P-value:			
	Fexo 20 mg bid	Fexo 60 mg bid	Fexo 120 mg bid	Fexo 240 mg bid	Placebo	Fexo 20 mg bid c/w placebo	Fexo 60 mg bid c/w placebo	Fexo 120 mg bid c/w placebo	Fexo 240 mg bid c/w placebo
Change from baseline in patient rated Mean Pruritus Score (=MPS, Score Range: 0-4) (Mean Difference ± [1]SE, % Δ from baseline) (Primary efficacy endpoint)									
Study 0039	-068 ± .09 (-37.8%)	-1.00 ± .08 (-53.8%)	-0.84 ± .08 (-43.3%)	-1.08 ± .08 (-56.5%)	-0.40 ± .08 (-18.8%)	0.0098	0.0001	0.0001	0.0001
Study 0067	-0.88 ± .07 (-47.6%)	-1.07 ± .07 (-54.0%)	-1.07 ± .07 (-52.5%)	-1.18 ± .07 (-65.2%)	-0.47 ± .07 (-24.5%)	0.0001	0.0001	0.0001	0.0001

[1]SE=Standard Error. P-values, means and associated std errors from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity.

Table IX. Summary of CIU Studies (0019) that Evaluated Once Daily (qd) Dosing of Fexofenadine [V1.207:89, 94]

	TREATMENT GROUPS					P-value:			
	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 180 mg qd	Fexo 240 mg qd	Placebo	Fexo 60 mg qd c/w placebo	Fexo 120 mg qd c/w placebo	Fexo 180 mg qd c/w placebo	Fexo 240 mg qd c/w placebo
Change from baseline in patient rated Mean Total Symptom Score (=composite score of the mean pruritus score (0-3 scale) + the mean # of wheals score (0-7 scale) or maximum total symptom score (Mean Difference ± [1]SE, % Δ from baseline) (Primary efficacy endpoint)									
Study 0019	-0.93 ± .3 (-23.7%)	-1.15 ± .3 (-26.6%)	-1.51 ± .2 (-48.7%)	-1.38 ± .3 (-33.8%)	-0.35 ± .3 (-9.6%)	0.1005	0.0670	0.0008	0.0041
Change from baseline in patient rated Mean Pruritus Score (0-3 scale): Post-hoc Analysis (from TSS above), Mean Difference ± [1]SE, % Δ from baseline)									
	-0.48 ± .1 (-27.3%)	-0.62 ± .1 (-32.0%)	-0.71 ± .1 (-42.0%)	-0.73 ± .1 (-41.7%)	-0.17 ± .1 (-27.3%)	0.0167	0.0120	0.0001	0.0001

[1]SE=Standard Error . P-values, means and associated std errors from an ANCOVA model containing adjustment for site, treatment, and baseline symptom

Review of these efficacy data showed a dose response for most fexofenadine doses for the 2 pivotal trials, ranging from 20 mg bid to 240 mg bid, which was statistically significant improvement for all bid doses of fexofenadine, as compared to placebo. These results were not replicated in study 0019, in which only the fexofenadine 180 mg and 240 mg qd doses demonstrated a significant improvement in the primary efficacy endpoint of the change from baseline in the mean total symptom score. Post-hoc analysis of the MPS for non-pivotal CIU study 0019 also revealed a statistically significant decrease in the MPS score for once daily fexofenadine doses ranging from 60 mg to 240 mg qd, compared to placebo. Of note, the % change in MPS score across active treatments was sizable (~ 24-65% decrease), however a large number of patients also discontinued treatment from each of these 3 trials (in some cases, up to 50%) due to 'lack of efficacy'. Hence, it is possible that these results represent 'enriched' efficacy data from antihistamine responders in CIU trials. Evaluation of the primary efficacy variable by demographic factors failed to show any difference in efficacy based on age, gender, or race. In study 0067, a statistically significant treatment-by-baseline interaction was seen at the 0.1 level (p=0.1080) in which patients with greater severity of symptoms demonstrated a greater response to treatment [V1.189:79].

Based on results of the 3 CIU trials, the most appropriate dose for treatment of CIU symptoms would appear to be the fexofenadine 60 mg bid dose since little added benefit was afforded by the higher fexofenadine doses with respect to decrease in pruritus or the number of wheals, althougth the 120 mg bid, and 240 mg bid or fexofenadine 180 mg qd and 240 mg qd doses also demonstrated statistically significant efficacy.

9.5. Onset of Action

Onset of action was only formally evaluated in 2 trials: (1) adult SAR trial 3081 and (2) combined pediatric SAR study 0066/0077.

For the adult SAR trial the daily change from baseline in patient self-rated 8:00 a.m. instantaneous TSS for the double-blind treatment period was evaluated, as shown in Table X. These data indicated an 'onset of action' by day 1, with maintenance of a statistically significant decrease in patient self-rated 8:00 a.m. instantaneous TSS compared to placebo up to day 4 of the study for both the fexofenadine 120 mg and 180 mg qd doses [V1.64:98-99]. Thus, in the adult study, analysis of the onset of action for the fexofenadine 120 mg and 180 mg doses failed to show a consistent sustained statistically significant decrease in the primary efficacy endpoint on a daily basis for the 2 week double-blind treatment period.

For the pediatric SAR combined trial, where the daily change from baseline in the 7:00 p.m. reflective TSS for the double-blind treatment period was evaluated, for the fexofenadine doses of 15 mg bid and 60 mg bid, a statistically significant decrease in the primary endpoint was seen by Day 2, although this was not maintained consistently thereafter. Throughout the 2-week double-blind period.

sporadic statistically significant improvement compared to placebo was seen for each of the 3 fexofenadine doses, but these were not maintained. These data are presented in Table XI.

Thus, while these 2 studies are informative in showing a statistically significant difference between fexofenadine and placebo treatment within 24 hours of dosing, previous chamber studies conducted with fexofenadine in a more controlled environment (with respect to pollen exposure) have narrowed down the onset of action for fexofenadine 60 mg bid to 1 hour. The analyses for onset of action taken from these 2 clinical efficacy studies, are supportive in showing an onset of effect within 1 day, but represent 'failed or inconclusive' studies with respect to showing consistent efficacy after an initial demonstration of effect.

Table X. **Onset of Action: Adult SAR (Study 3081)**
Efficacy of Fexofenadine HCl 120 mg, vs. Fexofenadine HCl 180 mg, vs. Placebo; DAILY CHANGE FROM BASELINE IN THE 8:00 a.m. INSTANTANEOUS TOTAL SYMPTOM SCORE FOR THE DOUBLE-BLIND TREATMENT PERIOD, ITT Population [V1.64:98-99]

	TREATMENT GROUP				
Efficacy Variable	**(A) Fexofenadine 120 mg qd**	**(B) Fexofenadine 180 mg qd**	**(C) Placebo**	**[1]P-value**	
				A-C	**B-C**
Change from Baseline in 8 a.m. Instantaneous Total Symptom Score: (N, Mean ± Standard Error)					
DAY 1	286 -0.87 ± 0.13	282 -0.88 ± 0.13	292 -0.29 ± 0.13	**0.0016**	**0.0014**
DAY 2	285 -0.87 ± 0.14	281 -1.06 ± 0.14	290 -0.32 ± 0.14	**0.0039**	**0.0001**
DAY 3	285 -0.95 ± 0.14	279 -1.01 ± 0.15	289 -0.41 ± 0.14	**0.0067**	**0.0028**
DAY 4	285 -1.06 ± 0.14	280 -1.00 ± 0.14	288 -0.69 ± 0.14	0.0574	0.1150
DAY 5	284 -1.00 ± 0.15	280 -1.30 ± 0.15	287 -0.78 ± 0.15	0.2914	**0.0106**
DAY 6	281 -1.12 ±0.15	279 -1.45 ± 0.15	287 -0.90 ± 0.15	0.2850	**0.0075**
DAY 7	278 -1.25 ± 0.15	272 -1.46 ± 0.15	283 -1.01 ± 0.15	0.2486	**0.0293**
DAY 8	275 -1.22 ± 0.15	268 -1.49 ± 0.16	278 -0.99 ± 0.15	0.2821	**0.0193**
DAY 9	274 -1.30 ± 0.15	265 -1.58 ± 0.15	274 -1.06 ± 0.15	0.2465	**0.0148**
DAY 10	274 -1.43 ± 0.16	265 -1.64 ± 0.16	276 -1.25 ± 0.16	0.3911	0.0747
DAY 11	274 -1.48 ± 0.16	263 -1.59 ± 0.16	275 -1.13 ± 0.16	0.1076	**0.0388**
DAY 12	268 -1.41 ± 0.16	256 -1.49 ± 0.17	269 -1.26 ± 0.16	0.5062	0.3114
DAY 13	235 -1.38 ± 0.17	224 -1.74 ± 0.17	245 -1.39 ± 0.17	0.9445	0.1425
DAY 14	99 -1.31 ± 0.31	110 -1.64 ± 0.29	110 -1.11 ± 0.29	0.6135	0.1647

[1]P-values for comparison of fexofenadine HCl doses to placebo, means, and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.

Table XI. **Onset of Action: Pediatric SAR (Studies 0066/0077 combined)**
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg vs. Placebo; DAILY CHANGE FROM BASELINE IN THE 7:00 p.m. REFLECTIVE TOTAL SYMPTOM SCORE (TSS) FOR THE DOUBLE-BLIND TREATMENT PERIOD, ITT Population [V1.225:91-93]

Efficacy Variable	TREATMENT GROUP (A) Fexo 15 mg qd	(B) Fexo 30 mg qd	(C) Fexo 60 mg qd	(D) Placebo	P-value[1] A-D	B-D	C-D
Change from Baseline in 8 a.m. Instantaneous Total Symptom Score: (N, Mean ± Standard Error)							
DAY 2	223 -1.16 ± 0.183	207 -0.81 ± 0.190	210 -1.13 ± 0.188	228 -0.62 ± 0.181	**0.0326**	0.4544	**0.0445**
DAY 3	222 -1.07 ± 0.189	208 -0.96 ± 0.196	209 -1.22 ± 0.195	226 -0.94 ± 0.188	0.6277	0.9490	0.2988
DAY 4	222 -1.29 ± 0.191	208 -1.19 ± 0.198	211 -1.28 ± 0.196	226 -0.88 ± 0.190	0.1154	0.2427	0.1283
DAY 5	222 -1.08 ± 0.203	207 -1.55 ± 0.211	211 -1.24 ± 0.208	228 -0.72 ± 0.200	0.1935	[redacted]	0.0676
DAY 6	221 -1.13 ±0.210	207 -1.20 ± 0.218	210 -1.45 ± 0.216	227 -0.81 ± 0.208	0.2588	0.1804	[redacted]
DAY 7	218 -1.33 ± 0.210	203 -1.61 ± 0.218	210 -1.33 ± 0.214	224 -0.91 ± 0.207	0.1439	[redacted]	0.1423
DAY 8	216 -1.68 ± 0.208	203 -1.36 ± 0.216	205 -1.58 ± 0.214	223 -1.11 ± 0.205	**0.0480**	0.4021	0.1098
DAY 9	214 -1.46 ± 0.220	201 -1.40 ± 0.229	205 -1.73 ± 0.225	221 -1.36 ± 0.218	0.7316	0.8887	0.2212
DAY 10	205 -1.94 ± 0.226	198 -1.74 ± 0.231	203 -1.72 ± 0.227	215 -1.62 ± 0.221	0.3030	0.6912	0.7574
DAY 11	209 -1.70 ± 0.222	200 -1.80 ± 0.228	205 -1.84 ± 0.224	215 -1.74 ± 0.219	0.9001	0.8461	0.7278
DAY 12	210 -1.95 ± 0.224	199 -1.78 ± 0.231	205 -1.98 ± 0.227	214 -1.98 ± 0.223	0.9167	0.5351	0.9996
DAY 13	211 -1.88 ± 0.228	201 -1.86 ± 0.235	203 -1.80 ± 0.232	212 -1.92 ± 0.228	0.9068	0.8694	0.7061
DAY 14	205 -2.09 ± 0.231	189 -2.20 ± 0.244	197 -1.83 ± 0.237	208 -2.00 ± 0.230	0.7928	0.5342	0.5949
DAY 15	103 -2.39 ± 0.362	85 -2.64 ± 0.400	95 -2.53 ± 0.384	104 -2.12 ± 0.367	0.5746	0.2932	0.4031
DAY 16	54 -2.06 ± 0.480	39 -3.06 ± 0.574	52 -2.55 ± 0.498	44 -1.38 ± 0.547	0.3311	[redacted]	0.0932

[1]P-values for comparison of fexofenadine HCl doses to placebo, adjusted means (LSMEANS), and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.

9.6. Quality of Life (Health Outcomes) Studies

A disease-specific quality of life assessment was conducted in each of the pivotal trials, for each of the 3 clinical indications in this NDA. These consisted of: (1) the Juniper Adult Rhinoconjunctivitis Questionnaire for adult SAR trial 3081, (2) the Juniper Pediatric Rhinoconjunctivitis Questionnaire for pediatric SAR trials 0066 and 0077, and (3) the Dermatology Quality of Life Index Questionnaire for the adult CIU studies 0039 and 0067. Both the adult and pediatric Juniper Rhinoconjunctivitis Questionnaire are deemed reasonable QOL instruments, but only the adult survey was able to demonstrate a consistent

statistically significant difference in fexofenadine 180 mg qd treated patients compared to placebo with respect to the primary analysis for the 2 weeks of double-blind treatment (primary endpoint=the overall RQLQ score or sum of the 7 individual domains) and the 7 individual domains. For pediatric study 0066/0077 combined in which the QOL analysis was performed, no significant effect on either the primary analysis or any of the 5 individual domains compared to placebo was seen for any of the 3 fexofenadine doses, with the exception of the 'other symptoms domain' for the fexofenadine 60 mg bid dose (p=.0459). For both the adult and pediatric QOL assessments, the nasal symptom domain appeared to contribute the greatest amount to the determination of the QOL score.

The clinically significant difference for the primary analysis was not specified in either the adult or pediatric QOL analysis, but for adult (but not pediatric) patient population the difference between the fexofenadine treatment arms and placebo was similar to the 'minimal important difference' (MID) seen in Elizabeth Juniper's original papers discussing these 2 tools for the evaluation of SAR in the circumstance where patients' rhinoconjunctivitis had changed (difference seen in adult QOL for the primary endpoint of overall QOL=0.57 and the difference seen in pediatric QOL for the primary endpoint of overall QOL=0.57) *(Juniper EF, Guyatt GH, Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis, Clin Exp Allergy, 1991, 21:77-83, Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ, Interpretation of rhinoconjunctivitis quality of life questionnaire data, JACI, 1996, 98:843-845, Juniper EF, Howland WC, Roberts NB, Thompson AK, and King ER, Measuring Quality of life in children with rhinoconjunctivitis, JACI, 1998, 101:164-169).* A summary of the change from baseline in adult and pediatric overall DLQI scores and individual SAR domains using the Juniper Questionnaire is presented in Tables XII. and XIII.

The dermatology QOL instrument used for the assessment of health outcomes in pivotal CIU studies 0039 and 0067 was one which was non-specific for CIU but deemed to be applicable to any skin disease—the Dermatology Quality of Life Index (DLQI). Consultation with the Division of Dermatologic Drug Products of FDA indicated that no CIU-specific instrument currently exists, and that in their experience the best measure of urticaria patients' QOL is the patient's self-rated pruritus score. Hence, the Division of Dermatologic Drug Products of FDA has not typically accepted QOL measures for this indication from sponsors for labeling or marketing purposes, unless truly disease-specific and as sensitive an endpoint as patients' self-rating of pruritus.

In addition, similar to the adult and pediatric SAR, no clinically relevant difference in primary analysis was specified by the sponsor with respect to the DLQI and CIU—a significant flaw in study design. Given this caveat, however, a statistically significant improvement in the overall DLQI score (the planned primary analysis) was seen for all 4 fexofenadine treatment arms in both CIU studies. Only the fexofenadine 60 mg qd, 120 mg qd, and 240 mg qd doses demonstrated a statistically significant improvement for the majority of the 6

individual DLQI domains. In the DLQI study, a significant treatment-by-baseline interaction was seen, with greater improvements noted in patients with higher baseline DLQI scores (i.e. more symptomatic patients). A summary of change in DLQI scores for studies 0039 and 0067 is presented in tables XIV. And XV.

Table XII. SAR Study 3081
Adult SAR QOL Analysis: Juniper Rhinoconjunctivitis Questionnaire
RQLQ SUMMARY: [1]Average Change from Baseline [V1.161:29, 31]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)	
	Fexo 120 mg qd	Fexo 180 mg qd
1. Overall DLQI Score (Planned Primary Analysis)	-0.57 ± .05 **(p=0.0059)**	-0.64 ± .05 **(p=0.0002)**
2. Miscellaneous Symptoms Domain	-0.12 ± .07 (p=0.0768)	-0.18 ± .07 **(p=0.0112)**
3. Activities Domain	-0.14 ± .09 (p=.1307)	-0.25 ± .09 **(p=0.0069)**
4. Sleep Domain	-0.12 ± .08 (p=0.1372)	-0.24 ± .08 **(p=0.0026)**
5. Practical Problems Domain	-0.25 ± .09 **(p=0.0037)**	-0.31 ± .09 **(p=0.0003)**
6. Emotions Domain	-0.21 ± .07 **(p=0.0048)**	-0.22 ± .07 **(p=0.0028)**
7. Eye Symptoms Domain	-0.17 ± .08 **(p=0.0378)**	-0.26 ± .08 **(p=0.0015)**
8. Nasal Symptom Domain	-0.26 ± .08 **(p=0.0012)**	-0.35 ± .08 **(p=0.0028)**

[1]Average of the data from Visit 2 and the final/early termination visit. Adjusted means (least square means), adjusted standard errors, and p-values from an ANCOVA containing site, treatment, baseline, and their interactions (if significant)

Table XIII. SAR Studies 0066/0077
Pediatric SAR QOL Analysis: Juniper Rhinoconjunctivitis Questionnaire (0-6 point scale)
RQLQ SUMMARY: [1]Average Change from Baseline [V1.255:30, 33-37]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)		
	Fexo 15 mg bid	Fexo 30 mg bid	Fexo 60 mg bid
1. Overall DLQI Score (Planned Primary Analysis)	-0.30 ± .05 (p=0.6401)	-0.38 ± .05 (p=0.5405)	-0.28 ± .05 (p=0.4298)
2. Nose Symptoms Domain	-0.39 ± .07 (p=0.8954)	-0.33 ± .07 (p=0.6197)	-0.37 ± .07 (p=0.9051)
3. Eye Symptoms Domain	-0.28 ± .07 (p=.9130)	-0.41 ± .07 (p=.1644)	-0.26 ± .07 (p=.9280)
4. Practical Problems Domain	-0.29 ± .06 (p=0.7466)	-0.35 ± .06 (p=0.6840)	-0.32 ± .06 (p=0.9946)
5. Other Symptoms Domain	-0.18 ± .06 (p=0.1580)	-0.33 ± .06 (p=0.7025)	-0.13 ± .06 **(p=0.0459)**
6. Activities Domain	-0.36 ± .07 (p=0.9534)	-0.39 ± .07 (p=0.8243)	-0.34 ± .07 (p=0.7749)

[1]Average of the data from Visit 2 and the final/early termination visit. Adjusted means (least square means), adjusted standard errors, and p-values from an ANCOVA containing site, treatment, baseline, and their interactions (if significant)

Table XIV. Adult CIU Study 0039: QOL Analysis
DLQI SUMMARY: [1]Average Change from Baseline [V1.217:49]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)			
	Fexo 20 mg qd	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 240 mg qd
1. Overall DLQI Score (Planned 1° Analysis)	-1.6590 ± .74947 (p=0.0386)	-2.959 ± .7982 (p=0.0002)	-2.420 ± .8227 (p=0.0035)	-3.706 ± .8170 (p=0.0001
2. Symptoms/Feelings Domain	-0.371 ± .2084 (p=0.0761)	-0.826 ± .2082 (p=0.0001)	-0.515 ± .2146 (p=0.0169)	-1.027 ± .2134 (p=0.0001)
3. Daily Activities Domain	-0.314 ± .1858 (p=.0921)	-0.645 ± .1861 (p=0.0006)	-0.488 ± .1925 (p=0.0116)	-0.697 ± .1906 (p=0.0003)
4. Leisure Domain	-0.291 ± .2193 (p=0.1861)	-0.675 ± .2204 (p=0.0024)	-0.582 ± .2258 (p=0.0104)	-0.807 ± .2248 (p=0.0004)
5. Work/school Domain	-0.132 ± .1041 (p=0.2043)	-0.376 ± .1053 (p=0.0004)	-0.251 ± .1082 (p=0.0208)	-0.469 ± .1071 (p=0.0001)
6. Personal Relations Domain	-0.435 ± .2091 (p=0.0382)	-0.448 ± .2100 (p=0.0336)	-0.390 ± .2161 (p=0.0721)	-0.531 ± .2149 (p=0.0140)
7. Treatment Domain	-0.114 ± .0938 (p=0.2236)	-0.118 ± .0945 (p=0.2122)	-0.067 ± .0969 (p=0.4909)	-0.164 ± .0974 (p=0.0939)

[1]Average of the data from Visit 2 and the final/early termination visit. Adjusted means (least square means), adjusted standard errors, and p-values from an ANCOVA containing site, treatment, baseline, and their interactions (if significant).

Table XV. Adult CIU Study 0067: QOL Analysis
DLQI SUMMARY: [1]Average Change from Baseline [V1.221:46]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)			
	Fexo 20 mg qd	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 240 mg qd
1. Overall DLQI Score (Planned 1° Analysis)	-2.021 ± .7625 (p=0.0085)	-3.192 ± .7962 (p=0.0001)	-3.220 ± .7693 (p=0.0001)	-3.415 ± .7913 (p=0.0001)
2. Symptoms/Feelings Domain	-0.779 ± .2016 (p=0.0001)	-0.945 ± .2127 (p=0.0001)	-1.007 ± .2043 (p=0.0169)	-1.406 ± .2099 (p=0.0001)
3. Daily Activities Domain	-0.323 ± .1801 (p=.0743)	-0.492 ± .1886 (p=0.0096)	-0.753 ± .1820 (p=0.0001)	-0.556 ± .1869 (p=0.0032)
4. Leisure Domain	-0.391 ± .2191 (p=0.0754)	-0.342 ± .2297 (p=0.1377)	-0.339 ± .2221 (p=0.1286)	-0.505 ± .2284 (p=0.0278)
5. Work/School Domain	-0.145 ± .1082 (p=0.1815)	-0.345 ± .1140 (p=0.0028)	-0.287 ± .1103 (p=0.0099)	-0.374 ± .1132 (p=0.0011)
6. Personal Relations Domain	-0.407 ± .2125 (p=0.0565)	-0.830 ± .2221 (p=0.0002)	-0.618 ± .2159 (p=0.0046)	-0.413 ± .2225 (p=0.0645)
7. Treatment Domain	-0.166 ± .0967 (p=0.0876)	-0.335 ± .1010 (p=0.0010)	-0.163 ± .0978 (p=0.0959)	-0.154 ± .1005 (p=0.1266)

[1]Average of the data from Visit 2 and the final/early termination visit. Adjusted means (least square means), adjusted standard errors, and p-values from an ANCOVA containing site, treatment, baseline, and their interactions (if significant).

10.0. Integrated Summary of Safety

The clinical experience and safety database with ALLEGRA is considerable, both from clinical trials and from marketing exposure. Clinical trial data supported FDA approval of ALLEGRA capsules, 60 mg (NDA 20-625) as a safe and effective treatment of nasal symptoms of SAR in adults and adolescents 12 years of age and older on 07/25/96. ALLEGRA capsules, 60 mg are also marketed in many countries worldwide.

Safety data from the original NDA (20-625) will not be reiterated in this review, the focus of which will be an evaluation of safety data from the 3 adult SAR studies conducted in patients 12 years of age and older, the 2 pediatric SAR studies conducted in children age 6-11 years of age, the 3 adult CIU studies, and the 1 year safety study conducted in healthy volunteers. The aim of this safety overview is to identify any new safety concerns with ALLEGRA tablet use, particularly at the higher than currently recommended doses such as 180 and 240 mg qd.

Hence, this safety analysis will consist of an overview of patient withdrawals, pooled adverse event frequencies (along with 'serious' adverse events) with close attention to the incidence of somnolence and to 'cardiac AEs', laboratory results and physical exam findings, cardiac evaluation (12 lead ECGs, with a focus on QTc intervals and detection of arrhythmias) based on the intent-to-treat population from studies performed for the 3 clinical indications sought in this NDA. Longer-term safety data in this ISS will come from one, U.S. (0027) 1-year safety study conducted in healthy volunteers who received either fexofenadine 240 mg qd or placebo (given as capsules). A primary focus of this 1 year study was evaluation of ECG changes over time.

A summary of all controlled clinical studies used in the ISS is presented in Table I. below:

Table I. Summary of Controlled Clinical Trials Reviewed in NDA 20-872 used in the Integrated Summary of Safety: ALLEGRA

STUDY	TREATMENT DURATION	TREATMENT ARMS:
Adult SAR		
3081-Pivotal Trial	2 weeks	Fexo: 120, 180 mg qd Placebo
0032	2 weeks	Fexo: 120, 180 mg qd, Cetirizine 10 mg qd, Placebo
0061	7-10 days	Fexo: 80, 120 mg qd, Placebo
Pediatric SAR		
Combined 0066/0077	2 weeks	Fexo: 15, 30, 60 mg bid, Placebo
Adult Chronic Idiopathic Urticaria (CIU)		
0039-Pivotal Trial	4 weeks	Fexo: 20, 60, 120, 240 mg bid, Placebo
0067-Pivotal Trial	4 weeks	Fexo: 20, 60, 120, 240 mg bid, Placebo
0019	6 weeks	Fexo: 60, 120, 240 mg qd, Placebo
Controlled, 1 year Safety Study		
0027	1 year	Fexo 240 mg qd, Placebo

10.1. Extent and Duration of Exposure

Extent and duration of exposure to fexofenadine was already delineated in the ISE but is re-iterated here in Table II. More than 200 patients received fexofenadine 240 mg qd--twice the currently marketed dose of fexofenadine for a 12 month duration. In addition, sufficient short-term safety data (i.e. 2-6 weeks) for each of the proposed clinical indications was obtained in each of the pivotal trials (adult SAR, pediatric SAR, and adult CIU).

Table II. Patient Exposure By Dose to ALLEGRA and Safety Evaluable Population; All Multiple-Dose Clinical Pharmacology and Controlled Clinical Trials [NDA 20-872, V1.298:60]

Dose	Controlled Studies								All Controlled Studies	
	Adult SAR		Adult CIU		Pediatric SAR		Normal Subjects			
	[1]Exp. n=2997	[2]SE n=2994	Exp. N=1131	SE N=1113	Exp. N=875	SE N=875	Exp. N=477	SE N=469	Exp. N=5477	SE N=5448
Placebo	945	944	234	229	229	229	237	235	1645	1638
Cetirizine	209	209	0	0	0	0	0	0	209	209
Fexofenadine Doses										
60 mg qd	0	0	44	44	0	0	0	0	44	44
80 mg qd	457	457	0	0	0	0	0	0	457	457
120 mg qd	960	959	38	38	0	0	0	0	998	997
180 mg qd	493	491	50	50	0	0	0	0	543	541
240 mg qd	0	0	39	39	0	0	240	234	279	273
15 mg bid	0	0	0	0	224	224	0	0	224	224
20 mg bid	0	0	188	187	0	0	0	0	188	187
30 mg bid	0	0	0	0	209	209	0	0	209	209
60 mg bid	0	0	191	186	213	213	0	0	404	399
120 mg bid	0	0	173	171	0	0	0	0	173	171
240 mg bid	0	0	174	169	0	0	0	0	174	169
Total Fexo	1889	1886	897	884	646	646	240	234	3669	3647

Analysis of patient/subject duration of exposure is presented in Table III below and reveals that most patients/subjects received < 30 days of fexofenadine treatment; and indeed most received close to 2 weeks of fexofenadine treatment since most trials reviewed in this NDA were designed with a 2 week duration of double-blind treatment. Of note, 598 patients/subjects received fexofenadine ≥ 30 days and of this group, 216 belonged to the 1-year safety study (0027). In the 1-year safety study the mean duration of exposure was 285.9 days for the placebo group and 271.2 days for the fexofenadine group [V1.259:48].

Table III: Duration of Fexofenadine Exposure [V1.298:45]

Duration of Exposure	Clinical Pharmacology		Controlled Studies				All Studies
	Normal Subjects (n=138)	Pediatric SAR (n=15)	Adult SAR (n=1889)	Adult CIU (n=897)	Pediatric SAR (n=646)	Normal Subjects (n=240)	(n=3822)
Single dose	123	15	0	0	0	0	138
Multiple dose < 30 days	24	0	1889	517	646	16	3092
Multiple dose ≥ 30 days	0	0	2	371	0	216	589
Unknown	0	0	21	10	0	8	39
N, Mean Days ± AD, Range	147, 6.3 ± 6.09, 1-20	15, 1.9 ± .35, 1-2	1891, 12.8 ± 2.97	888, 28.0 ± 10.14, 1-73	646, 15.5 ± 1.98, 1-22	232, 272.2 ± 120.18, 2-377	3819, 32.2 ± 68.48, 1-377

10.2. Patient Demographics

A total of 4740 adult patients were enrolled in the various studies in NDA 20-872, of whom 3161 received various doses of fexofenadine. A summary of patient characteristics for the adult trials is summarized in Table IV. and overall indicates similar patient demographics across treatments. A similar analysis performed in pediatric patients is summarized in Table V and also indicates similar demographic characteristics across treatments.

Table IV. Patient Demographics of All [1]Adult Studies Combined (Clinical Pharmacology and Controlled Studies) [V1.298:51]

	Adult Clinical Pharmacology and Controlled Studies			
Characteristics	**Placebo (n=1416)**	**Fexofenadine (n=3161)**	**Cetirizine (n=209)**	**Total (n=4740)**
Gender (n, %)				
Male	632 (44.6%)	1426 (45.1%)	102 (48.8%)	2128 (44.9%)
Female	784 (55.4%)	1735 (54.9%)	107 (51.2%)	2612 (55.1%)
Age (Years)				
n	1416	3161	209	4740
Mean ± SD	33.6 ± 12.2	34.0 ± 12.6	32.8 ± 11.9	33.8 ± 12.5
Range	12-81	12-84	12-62	12-84
12 to < 16	87 (6.1%)	172 (5.4%)	7 (3.3%)	266 (5.6%)
16 to < 40	892 (63.0%)	1973 (62.4%)	140 (67.0%)	2979 (62.8%)
40 to < 65	427 (30.2%)	982 (31.1%)	62 (29.7%)	1451 (30.6%)
≥ 65	10 (0.7%)	34 (1.1%)	0 (0.0%)	44 (0.9%)
Race (n, %)				
Caucasian	1297 (91.6%)	2860 (90.5%)	186 (89.0%)	4298 (90.7%)
Black	54 (3.8%)	136 (4.3%)	5 (2.4%)	195 (4.1%)
Asian	31 (2.2%)	97 (3.1%)	7 (3.3%)	134 (2.8%)
Multiracial	34 (2.4%)	68 (2.2%)	11 (5.3%)	113 (2.4%)
Weight (kg)				
n	1411	3157	209	4731
Unknown n	5	4	0	9
Mean ± SD	72.7 ± 17.0	72.8 ± 16.5	71.7 ± 16.5	72.7 ± 16.1
Range	32.2-167	31-155.1	43-147	31-167
< 60	328 (23.2%)	698 (22.1%)	50 (23.9%)	1069 (22.6%)
60 to > 90	881 (62.4%)	1983 (62.8%)	135 (64.6%)	2969 (62.8%)
≥ 90	202 (14.3%)	476 (15.1%)	24 (11.5%)	693 (14.6%)

[1]Adult studies summarized in this table include: clinical pharmacology studies 033, part 2, 045, 062, 071, 068, 022, controlled SAR trials 3081, 0032, 0061, CIU studies 0039, 0067, 0019, and controlled normal subject 1 year safety study 0027.

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Table V. Patient Demographics of All [1]Pediatric Studies Combined (Clinical Pharmacology and Controlled Studies) [V1.298:52]

Characteristics	Pediatric Clinical Pharmacology and Controlled Studies		
	Placebo (n=229)	Fexofenadine (n=661)	Total (n=4740)
Gender (n, %)			
Male	139 (60.7%)	391 (60.7%)	530 (59.6%)
Female	90 (39.3%)	270 (40.8%)	360 (40.4%)
Age (Years)			
n	229	661	890
Mean ± SD	9.2 ± 1.6	9.1 ± 1.6	9.1 ± 1.6
Range	6-11	5-12	5-12
6 to < 9	77 (33.6%)	217 (32.8%)	294 (33.0%)
9 to 12	152 (66.4%)	444 (67.2%)	596 (67.0%)
Race (n, %)			
Caucasian	187 (81.7%)	577 (87.3%)	764 (85.8%)
Black	28 (12.2%)	53 (8.0%)	81 (9.1%)
Asian	7 (3.1%)	12 (1.8%)	19 (2.1%)
Multiracial	7 (3.1%)	19 (2.9%)	26 (2.9%)
Weight (kg)			
n	229	656	885
Unknown n	0	5	5
Mean ± SD	36.6 ± 11.1	35.3 ± 10.8	35.6 ± 10.9
Range	21-77.1	0 (0%)	17.7-93
< 15	0 (0%)	17.7-93	0 (0%)
15 to < 30	76 (33.2%)	239 (36.4%)	315 (35.6%)
30 to < 45	112 (48.9%)	321 (48.9%)	433 (48.9%)
≥ 45	41 (17.9%)	96 (14.6%)	137 (15.5%)

[1]Pediatric studies summarized in this table include: clinical pharmacology study 037, and controlled SAR trials 0066 and 0077.

Slightly more female than male patients participated in the adult studies, in contrast slightly more male than female patients participated in the pediatric studies. For both the adult and pediatric populations, the majority of patients were Caucasian. For the adult group, most patients ranged from 16 to < 40 years of age. In the pediatric age group, a greater proportion (~ 2/3) of enrolled patients belonged to an older (age 9-12 year) age group, however children 6 years of age and above were represented in all treamtent groups studied.

A more complete break down of adult and pediatric population demographics by study type (i.e. controlled SAR, CIU studies, etc). is provided in attached Tables 8-202 and 8-204 from the NDA submission [V1.298:49-50, 52].

10.3. Patient Disposition

The patient disposition for the 3 different clinical indications in this NDA is summarized in 3 different tablets below (Tables VI, VII, and VIII). For all 3 indications the % of patients that discontinued treatment due to an adverse event (AE) due to fexofenadine treatment (especially for all fexofenadine doses for a given indication; a 0.8-3.6% discontinuation rate due to AEs for fexofenadine doses combined) was generally lower than for the placebo treatment group (range of 2.2-3.9% across indications). More frequently than AEs, most patients appeared to discontinue treatment across indications due to either 'other reasons' or treatment failure. The overall % of patients discontinuing treatment was fairly

Table 8-202: Demographics of the Adult Patient Population (and Healthy Subjects), [V1.298:49-50]

Table 8-202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
Page 1 of 2

Characteristics	Clinical pharmacology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Gender n(%)											
Male	138 (100%)	459 (48.6%)*	914 (48.4%)	102 (48.8%)	1443 (48.1%)	71 (30.3%)	275 (30.7%)	346 (30.6%)	102 (43.0%)	99 (41.3%)	201 (42.1%)
Female	0 (0.0%)	486 (51.4%)	975 (51.6%)	107 (51.2%)	1554 (51.9%)	163 (69.7%)	622 (69.3%)	785 (69.4%)	135 (57.0%)	141 (58.8%)	276 (57.9%)
Age (years) n(%)											
N	138	945	1889	209	2997	234	897	1131	237	240	477
Mean ± SD	27.7 ± 6.7	32.2 ± 11.7	31.8 ± 12.0	32.8 ± 11.9	31.9 ± 11.9	39.3 ± 13.4	39.5 ± 12.7	39.5 ± 12.8	33.4 ± 11.4	34.7 ± 13.0	34.0 ± 12.2
Range	18,44	12,85	12,70	12,82	12,70	13,81	12,84	12,84	12,85	12,84	12,85
12–<16	0 (0.0%)	64 (6.8%)	141 (7.5%)	7 (3.3%)	212 (7.1%)	6 (3.4%)	15 (1.7%)	23 (2.0%)	15 (6.3%)	16 (6.7%)	31 (6.5%)
16–<40	130 (94.2%)	627 (66.3%)	1256 (66.5%)	140 (67.0%)	1997 (66.6%)	113 (48.3%)	447 (49.8%)	560 (49.5%)	152 (64.1%)	142 (59.2%)	294 (61.6%)
40–<65	8 (5.8%)	251 (26.6%)	482 (25.5%)	62 (29.7%)	775 (25.9%)	107 (45.7%)	411 (45.8%)	518 (45.8%)	69 (29.1%)	82 (34.2%)	151 (31.7%)
≥ 65	0 (0.0%)	3 (0.3%)	10 (0.5%)	0 (0.0%)	13 (0.4%)	6 (2.6%)	24 (2.7%)	30 (2.7%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Race n(%)											
Caucasian	126 (91.3%)	868 (91.8%)	1714 (90.7%)	186 (89.0%)	2721 (90.8%)	216 (92.3%)	799 (89.1%)	1015 (89.7%)	215 (90.7%)	223 (92.9%)	438 (91.8%)
Black	7 (5.1%)	36 (3.8%)	79 (4.2%)	5 (2.4%)	120 (4.0%)	10 (4.3%)	43 (4.8%)	53 (4.7%)	8 (3.4%)	7 (2.9%)	15 (3.1%)
Asian	3 (2.2%)	22 (2.3%)	49 (2.6%)	7 (3.3%)	77 (2.6%)	4 (1.7%)	39 (4.3%)	43 (3.8%)	5 (2.1%)	7 (2.9%)	12 (2.5%)
Multiracial	2 (1.4%)	21 (2.2%)	47 (2.5%)	11 (5.3%)	79 (2.6%)	4 (1.7%)	16 (1.8%)	20 (1.8%)	9 (3.8%)	3 (1.3%)	12 (2.5%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 061, 032, 061
Controlled CIU = Protocols 039, 057, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 061, one placebo patient was inadvertently reported as a male, but should be female.

Table 8-202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
Page 1 of 2

Characteristics	Clinical pharmacology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Gender n(%)											
Male	138 (100%)	459 (48.6%)*	914 (48.4%)	102 (48.8%)	1443 (48.1%)	71 (30.3%)	275 (30.7%)	346 (30.6%)	102 (43.0%)	99 (41.3%)	201 (42.1%)
Female	0 (0.0%)	486 (51.4%)	975 (51.6%)	107 (51.2%)	1554 (51.9%)	163 (69.7%)	622 (69.3%)	785 (69.4%)	135 (57.0%)	141 (58.8%)	276 (57.9%)
Age (years) n(%)											
N	138	945	1889	209	2997	234	897	1131	237	240	477
Mean ± SD	27.7 ± 6.7	32.2 ± 11.7	31.8 ± 12.0	32.8 ± 11.9	31.9 ± 11.9	39.3 ± 13.4	39.5 ± 12.7	39.5 ± 12.8	33.4 ± 11.4	34.7 ± 13.0	34.0 ± 12.2
Range	18,44	12,85	12,70	12,82	12,70	13,81	12,84	12,84	12,85	12,84	12,85
12–<16	0 (0.0%)	64 (6.8%)	141 (7.5%)	7 (3.3%)	212 (7.1%)	8 (3.4%)	15 (1.7%)	23 (2.0%)	15 (6.3%)	16 (6.7%)	31 (6.5%)
16–<40	130 (94.2%)	627 (66.3%)	1256 (66.5%)	140 (67.0%)	1997 (66.6%)	113 (48.3%)	447 (49.8%)	560 (49.5%)	152 (64.1%)	142 (59.2%)	294 (61.6%)
40–<65	8 (5.8%)	251 (26.6%)	482 (25.5%)	62 (29.7%)	775 (25.9%)	107 (45.7%)	411 (45.8%)	518 (45.8%)	69 (29.1%)	82 (34.2%)	151 (31.7%)
≥ 65	0 (0.0%)	3 (0.3%)	10 (0.5%)	0 (0.0%)	13 (0.4%)	6 (2.6%)	24 (2.7%)	30 (2.7%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Race n(%)											
Caucasian	126 (91.3%)	868 (91.8%)	1714 (90.7%)	186 (89.0%)	2721 (90.8%)	216 (92.3%)	799 (89.1%)	1015 (89.7%)	215 (90.7%)	223 (92.9%)	438 (91.8%)
Black	7 (5.1%)	36 (3.8%)	79 (4.2%)	5 (2.4%)	120 (4.0%)	10 (4.3%)	43 (4.8%)	53 (4.7%)	8 (3.4%)	7 (2.9%)	15 (3.1%)
Asian	3 (2.2%)	22 (2.3%)	49 (2.6%)	7 (3.3%)	77 (2.6%)	4 (1.7%)	39 (4.3%)	43 (3.8%)	5 (2.1%)	7 (2.9%)	12 (2.5%)
Multiracial	2 (1.4%)	21 (2.2%)	47 (2.5%)	11 (5.3%)	79 (2.6%)	4 (1.7%)	16 (1.8%)	20 (1.8%)	9 (3.8%)	3 (1.3%)	12 (2.5%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 061, 032, 061
Controlled CIU = Protocols 039, 057, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 061, one placebo patient was inadvertently reported as a male, but should be female.

Table 8-204: Demographic Characteristics of the Pediatric Population (Studies 0066/0077 combined) [V1.298:52]

Table 8–202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
Page 2 of 2

Charac-teristics	Clinical pharma-cology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Weight (kg) n(%)											
Unknown (N)	0	3	3	0	6	2	1	3	0	0	0
N	138	942	1886	209	2991	232	896	1128	237	240	477
Mean ± SD	76.7 ± 9.7	71.7 ± 16.5	71.4 ± 16.0	71.7 ± 16.5	71.5 ± 16.2	76.0 ± 18.9	75.4 ± 18.1	75.5 ± 18.2	73.5 ± 16.5	72.3 ± 16.0	72.9 ± 16.2
Range	57.15,99.34	32.2,167	31,145	43,147	31,167	46.9,149.7	32.2,155.1	32.2,155.1	42.525,131.4	44.1,124.65	42.525,131.4
<60	6 (4.3%)	226 (24.0%)	453 (24.0%)	50 (23.9%)	723 (24.2%)	48 (20.7%)	183 (20.4%)	231 (20.5%)	54 (22.8%)	57 (23.8%)	111 (23.3%)
60–<90	117 (84.8%)	597 (63.4%)	1180 (62.6%)	135 (64.6%)	1879 (62.8%)	136 (58.6%)	536 (59.8%)	672 (59.6%)	148 (62.4%)	152 (63.3%)	300 (62.9%)
≥90	15 (10.9%)	119 (12.6%)	253 (13.4%)	24 (11.5%)	389 (13.0%)	48 (20.7%)	177 (19.8%)	225 (19.9%)	35 (14.8%)	31 (12.9%)	66 (13.8%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 061, 032, 061
Controlled CIU = Protocols 039, 067, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 061, one placebo patient was inadvertently reported as a male, but should be female.

Supporting Data: *Page*

high for all adult SAR trials combined (~10 % across treatment groups) and even higher for the adult CIU trials 0039 and 0067 combined (15-30% range across treatments, with the highest discontinuation rate noted in the placebo group). In CIU, the primary reason for discontinuation, which contributed to the relatively high rate, was treatment failure.

Table VI: Patient Discontinuation for all Controlled Adult QD SAR Trials (3081, 0032, 0061), ITT Population [V1.299:88]

	TREATMENT GROUP					
	Fexo 60 mg qd (n=457)[1]	Fexo 120 mg qd (n=959)	Fexo 180 mg qd (n=491)	All Fexo Doses (n=1886)	Cetirizine 10 mg qd (n=209)	Placebo (n=944)
Reason for Discontinuation						
Adverse event	5 (1.1%)	25 (2.6%)	13 (2.6%)	43 (2.3%)	2 (1.0%)	31 (3.3%)
Elected to discontinue	29 (6.3%)	37 (3.9%)	7 (1.4%)	73 (3.9%)	2 (1.0%)	48 (5.1%)
Treatment Failure	16 (3.5%)	28 (2.9%)	18 (3.7%)	62 (3.3%)	7 (3.3%)	44 (4.7%)
Other	10 (2.2%)	26 (2.7%)	19 (3.9%)	55 (2.9%)	10 (4.8%)	34 (3.6%)
ALL REASONS	57 (12.5%)	103 (10.7%)	45 (9.2%)	204 (10.8%)	21 (10.0%)	135 (14.3%)

[1]n=number of randomized patients at the time of study initiation.

Table VII: Patient Discontinuation for Pediatric BID SAR (0066, 0077), ITT Population [V1.299:91]

	TREATMENT GROUP				
	Fexo 15 mg bid (n=224)[1]	Fexo 30 mg bid (n=209)	Fexo 60 mg bid (n=213)	All Fexo Doses (n=646)	Placebo (n=229)
Reason for Discontinuation					
Adverse event	1 (0.4%)	3 (1.4%)	1 (0.5%)	5 (0.8%)	5 (2.2%)
Elected to discontinue	2 (0.9%)	0 (0.0%)	1 (0.5%)	3 (0.5%)	4 (1.7%)
Treatment Failure	4 (1.8%)	3 (1.4%)	2 (0.9%)	9 (1.4%)	4 (1.7%)
Other	3 (1.3%)	2 (1.0%)	1 (0.5%)	6 (0.9%)	0 (0.0%)
ALL REASONS	10 (4.5%)	8 (3.8%)	5 (2.3%)	23 (3.6%)	13 (5.7%)

[1]n=number of randomized patients at the time of study initiation.

Table VIII : Patient Discontinuation for all Controlled Adult BID (U.S.) CIU Trials (0039, 0067), ITT Population [V1.299:90]

	TREATMENT GROUP					
	Fexo 20 mg bid (n=187)[1]	Fexo 60 mg bid (n=186)	Fexo 120 mg bid (n=171)	Fexo 240 mg bid (n=169)	All Fexo Doses (n=713)	Placebo (n=178)
Reason for Discontinuation						
Adverse event	8 (4.3%)	9 (4.8%)	7 (4.1%)	2 (1.2%)	26 (3.6%)	7 (3.9%)
Elected to discontinue	2 (1.1%)	2 (1.1%)	3 (1.8%)	4 (2.4%)	11 (1.5%)	3 (1.7%)
Treatment Failure	21 (11.2%)	11 (5.9%)	11 (6.4%)	7 (4.1%)	50 (7.0%)	35 (19.7%)
Other	17 (9.1%)	10 (5.4%)	5 (2.9%)	14 (8.3%)	46 (6.5%)	9 (5.1%)
ALL REASONS	48 (25.7%)	32 (17.2%)	26 (15.2%)	27 (16.0%)	133 (18.7%)	54 (30.3%)

[1]n=number of randomized patients at the time of study initiation.

10.4. Adverse Event Frequency

Review of adverse events (AEs) experienced by patients for the 3 different ALLEGRA indications revealed similar AE profiles and frequencies for the 2 SAR indications (Adult qd and Pediatric bid), with headache, upper respiratory infection (URI), and pharyngitis ranking as the top 3 AEs, although the overall difference in frequency was not significantly different from placebo treatment. These results are presented in Tables IX, X, and XI. AEs that were ≥ 2% in frequency for fexofenadine treatment and that were more common than placebo consisted of the following: (1) for adult qd SAR: back pain, and (2) for pediatric bid SAR: coughing, injury accident, fever, pain, and otitis media. For the adult CIU indication, headache, URI, and pharyngitis were likewise the 3 most frequent AEs but the incidence of these was also similar to that of the placebo group. AEs that were ≥ 2% in incidence for the fexofenadine groups but higher than placebo consisted of: sinusitis, dizziness, somnolence, and back pain. The incidence of somnolence across indications was very low for fexofenadine treated patients, even in the combined CIU studies were the incidence ranged from 1.2-2.3%). A dose response for somnolence was not seen across fexofenadine treatments. A total of 4 patients across all controlled clinical studies submitted to this NDA withdrew from study participation due to somnolence (1 patient taking fexofenadine 180 mg qd in adult SAR study 3081, 1 patient taking fexofenadine 60 mg bid and 1 patient taking fexofenadine 240 mg bid in CIU study 0039, and 1 patient taking fexofenadine 120 mg bid in CIU study 0067 [V1.80:84, V1.170:1227, V1.180:120].

Review of cardiac AEs failed to reveal a higher incidence of chest pain, ventricular arrhythmia, tachycardia, palpitations, and syncope in fexofenadine treated patients over placebo patients. The most common AE for withdrawal from studies across indications was headache.

Subgroup analysis of AEs for the 3 different indications revealed no gender difference in the types of AEs reported between males and females, though female patients did report a slightly higher overall frequency of AEs for each

respective treatment arm compared to male patients [V1.298:124-135, 221-230, V1.299:15-17].

When examined across different age groups for the adult and adolescent populations, defined as: 12 < 16 years of age, 16 < 40 years of age, 40 < 65 years of age and ≥ 65 years of age, the percentage of patients experiencing AEs was similar amongst the 4 different age groups [V1.298:136-152, 231-246]. For the pediatric age group (studies 0066/0077): the 5 < 9 years of age and the 9 to ≤ 12 years of age group, the overall incidence, as well as individual AE incidences was higher in the 5 < 9 years of age group, compared to placebo [V1.288:18-21].

Adverse event frequency by ethnic origin was somewhat difficult to interpret, as the majority of all patients evaluated in all studies (for the 3 indications) were Caucasian. The number of patients in the other ethnic groups were again too small to draw conclusions. Nonetheless, for the Caucasian group, the most frequent AEs consisted of headaches, URI, and pharyngitis; again similar to the AE profile for the total population of SAR and CIU patients evaluated in this NDA submission [V1.298:122, 248-262, 299:22-25].

Table IX: Adverse Event (AE) Frequency: Controlled U.S. Adult SAR Trials (3081) AE's ≥ 2% for ALLEGRA (Fexofenadine 120 mg, Fexofenadine 180 mg, vs. Placebo), by Organ System and Preferred Term; Safety Evaluable Population [V1.64:118-121, V1.298:100-102, 104]

BODY SYSTEM	Preferred Term	Fexofenadine HCl 120 mg (n=287) n (%)	Fexofenadine HCl 180 mg (n=283) n (%)	Placebo (n=293) n (%)
All Systems	Any AE	86 (30.0%)	86 (30.4%)	88 (30.0%)
Neurologic	**Headache**	**21 (7.3%)**	**30 (10.6%)**	**22 (7.5%)**
Respiratory	Upper respiratory tract infection	6 (2.1%)	9 (3.2%)	9 (3.1%)
	Pharyngitis	8 (2.8%)	6 (2.1%)	9 (3.1%)
Body as a Whole-General	Back Pain	8 (2.8%)	8 (2.8%)	4 (1.4%)
	Pain	7 (2.4%)	5 (1.8%)	10 (3.4%)
Musculoskeletal	Myalgia	3 (1.0%)	8 (2.8%)	9 (3.1%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

Table X: Adverse Event (AE) Frequency: Pediatric SAR Studies (0066 and 0077) AE's ≥ 2% for ALLEGRA (Fexofenadine 15 mg, 30 mg, and 60 mg bid vs. Placebo), by Organ System and Preferred Term; Safety Evaluable Population [V1.225:99-102, 244:51-54]

BODY SYSTEM	Preferred Term	Fexo 15 mg (n=224) n (%)	Fexo 30 mg (n=209) n (%)	Fexo 60 mg (n=213) n (%)	Placebo (n=229) n (%)
All Systems	Any AE	79 (35.3%)	77 (36.8%)	74 (34.7%)	83 (36.2%)
Neurologic	**Headache**	**18 (8.0%)**	**15 (7.2%)**	**20 (9.4%)**	**15 (6.6%)**
Respiratory	Upper respiratory tract infection	11 (4.9%)	9 (4.3%)	3 (1.4%)	4 (1.7%)
	Pharyngitis	9 (4.0%)	6 (2.9%)	6 (2.8%)	9 (3.9%)
	Coughing	3 (1.3%)	8 (3.8%)	5 (2.3%)	3 (1.3%)
Body as a Whole-General	Injury Accident	4 (1.8%)	6 (2.9%)	9 (4.2%)	3 (1.3%)
	Abdominal Pain	6 (2.7%)	4 (1.9%)	5 (2.3%)	8 (3.5%)
	Fever	4 (1.8%)	5 (2.4%)	4 (1.9%)	2 (0.9%)
	Pain	0 (0.0%)	5 (2.4%)	4 (1.9%)	1 (0.4%)
Hearing and Vestibular	Otitis media	1 (0.4%)	5 (2.4%)	2 (0.9%)	0 (0.0%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

Table XI: Adverse Event Frequency ≥ 2% for All Controlled (U.S.) Fexofenadine BID Dosing Adult CIU Studies (0039 and 0067) Safety Evaluable Population [NDA 20-872, V1.298:201-206]

Adverse Event	Placebo (n=187)	Fexo 20 mg bid (n=187)	Fexo 60 mg bid (n=186)	Fexo 120 mg bid (n=171)	Fexo 240 mg bid (n=169)
Any AE	109 (59.0%)	124 (66.3%)	108 (58.1%)	107 (62.6%)	102 (60.4%)
Headache	**34 (19.1%)**	**51 (27.3%)**	**34 (18.3%)**	**39 (22.8%)**	**33 (19.5%)**
URI	**15 (8.4%)**	**12 (6.4%)**	**13 (7.0%)**	**22 (12.9%)**	**15 (8.9%)**
Pharyngitis	**10 (5.6%)**	**11 (5.9%)**	**8 (4.3%)**	**5 (2.9%)**	**11 (6.5%)**
Dyspepsia	9 (5.1%)	9 (4.8%)	8 (4.8%)	6 (3.5%)	7 (4.1%)
Pain	11 (6.2%)	7 (3.7%)	9 (4.8%)	5 (2.9%)	5 (3.0%)
Upper Respiratory Congestion	6 (3.4%)	2 (1.1%)	6 (3.2%)	2 (1.2%)	6 (3.6%)
Rhinitis	9 (5.1%)	8 (4.3%)	6 (3.2%)	5 (2.9%)	4 (2.4%)
Diarrhea	6 (3.4%)	5 (2.7%)	6 (3.2%)	2 (1.2%)	5 (3.0%)
Nausea	7 (3.9%)	11 (5.9%)	5 (2.7%)	8 (4.7%)	11 (6.5%)
Influenza	5 (2.8%)	9 (4.8%)	5 (2.7%)	6 (3.5%)	6 (3.6%)
Sinusitis	2 (1.1%)	5 (2.7%)	4 (2.2%)	6 (3.5%)	3 (1.8%)
Dizziness	1 (0.6%)	2 (1.1%)	4 (2.2%)	5 (2.9%)	3 (1.8%)
Somnolence	0 (0.0%)	3 (1.6%)	4 (2.2%)	4 (2.3%)	2 (1.2%)
Back Pain	1 (1.1%)	4 (2.1%)	4 (2.2%)	3 (1.8%)	5 (3.0%)
Myalgia	5 (2.8%)	7 (3.7%)	4 (2.2%)	4 (2.3%)	7 (4.1%)
Arthralgia	3 (1.7%)	7 (3.7%)	2 (1.1%)	2 (1.2%)	4 (2.4%)
Insomnia	2 (1.1%)	4 (2.1%)	2 (1.1%)	4 (2.3%)	5 (3.0%)
Dysmenorrhea	3 (1.7%)	4 (2.1%)	2 (1.1%)	5 (2.9%)	5 (3.0%)
Fatigue	4 (2.2%)	1 (0.5%)	1 (0.5%)	4 (2.3%)	0 (0.0%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

When long-term exposure (i.e. up to 1 year) of 240 healthy adults and adolescents ≥ 12 years of age to once daily fexofenadine 240 mg qd was assessed

in study 0027, while AEs overall were higher in number (because of the longer study trial duration than either the SAR or CIU trials), headache still remained the most common AE. This however, was followed in frequency by viral infection (in current ALLEGRA label). Cardiac AEs (QT interval prolongation, chest pain, dizziness, syncope, and ECG abnormality (specific and non-specific) were similar in incidence between the fexofenadine 240 mg qd and placebo group.

A comparison of the adverse event profile from the adult SAR clinical trials and the approved package insert for ALLEGRA 60 mg capsules (SAR indication in adults), indicates that the AE frequencies for fexofenadine were similar between the tablet and capsule and at the higher dose (120 mg and 180 mg), with the major exception that viral infection was not noted to have a high incidence in the adult SAR trials (of note, as higher incidence than in pediatric SAR and adult CIU trials). Nonetheless, the AE profiles for controlled U.S. adult and pediatric SAR studies and the CIU trials are slightly different, with different doses of ALLEGRA tablets proposed as the treatment dose, hence the medical reviewer recommends including the AE database (≥ 2% incidence) for each of these 3 clinical indications in the label for ALLEGRA tablets.

10.5. Serious Adverse Events

When having excluded all adverse events treated with a counteractive medication that were also cited as serious adverse events, in addition to the usual regulatory definition, relatively few serious AEs were noted across studies reviewed in this NDA submission. Furthermore, review of serious AEs across trials indicated that most were not related to study medication (refer to appropriate sections of each study). A list of serious AEs for the adult qd SAR trials, the pediatric trials, and the CIU trials are summarized in Tables 8-281 of the NDA submission [V1.299:115,118, 119] and show a general tendency for placebo-treated patients to have a slightly greater incidence of serious AEs than fexofenadine treated patients.

Only 1 death was reported in this NDA, in a healthy volunteer receiving placebo and participating in the 1 year safety study 0027—due a self-inflicted gunshot wound that was not deemed related to study medication [V1.259:66].

10.6. Laboratory Tests

Review of laboratory tests for all studies reviewed in this submission (including 1 year safety study 0027) by means, shift tables, and outlier results showed no trends or dose responses with fexofenadine treatment. While the more frequently reported laboratory abnormalities across studies involved changes in white blood cell, lymphocyte, and neutrophil counts and less frequently liver function tests (SGPT, total bilirubin), and serum triglyceride with fexofenadine treatment, approximately equal numbers of high and low values were reported, with no discernible pattern seen [V1.299;152-229].

10.7. Physical Exam Findings

Routine physical exams findings were not tabulated in any manner in order to assess change from baseline from the safety perspective. Abnormal physical exam findings were provided as line listings, and review of these failed to show any worrisome findings or trends. Furthermore, based on the mechanism of action of fexofenadine, one would not expect any discrete physical exam findings with use of this medication. event reporting, followed by physical exam.

10.8. Vital Signs

Vital signs (systolic (SBP) and diastolic BP (DBP), heart rate (HR) were evaluated in all the clinical trials submitted to this NDA and overall few outlier values were reported. Of those that were, most were borderline. Evaluation of the mean change in vital signs across clinical trials revealed very small, clinically insignificant decreases in SBP and DBP and increases in HR in adult SAR trials 3081, 0032, and 0061, pediatric SAR trials 0066/0077, and CIU trials 0039 and 0067 [V.299:261-271]. In the 1-year safety study (0027), very small decreases in SBP and DBP and small increases in HR were also seen for both the placebo treatment group and the fexofenadine 240 mg qd group. A slight increase in DBP was seen in the fexofenadine 240 mg qd group compared to placebo. No dose response with respect to these changes was seen in any of these studies (i.e. no dose-related trends noted), including the 1 year safety study. Thus, based on vital sign data from this NDA, along with clinical safety data from NDA 20-625, there is no reason to suspect that this medication would significantly alter the hemodynamics of patients taking this medication.

10.9. 12-Lead ECGs

12-lead ECGs were performed pre- and post-dosing with study medication in 3 studies in NDA 20-872: (1) placebo-controlled CIU study 0019, (2) placebo-controlled combined pediatric SAR studies 0066/0077, and (3) in the 1-year safety study in healthy volunteers. None of these 3 studies showed evidence of a QTc prolonging effect with fexofenadine use, even when dosed at twice the currently labelled dose for up to 1 year. While the 1-year safety study showed a statistically significant difference in maximum-postbaseline ECG values for fexofenadine 240 mg po qd vs. placebo, these numerical differences were < 4 msec and importantly, the effect of active drug was less than that of placebo. In the pediatric SAR studies, the number of QTc outliers for any of the 3 fexofenadine doses was lower in terms of % than that of the placebo group.

It is important to note that for the pediatric study in particular, patients who had evidence of QTc prolongation on entry were excluded from study participation, hence these studies by design were not able to specifically answer the question of whether patients with underlying QTc prolongation due to a variety of etiologies (e.g. cardiovascular disease, congenital prolonged QT syndrome, etc.) would have demonstrated similar ECG results.

A summary of ECG data from these 3 studies is presented in Tables XII- XVII below.

Table XII: Controlled CIU Study (0019)
Mean QT_c Change from Baseline for Fexofenadine 60 mg, 120 mg, 180 mg, and 240 mg qd, compared to Placebo [V1.299:248]

ECG Parameter	Treatment (qd)	[1]n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	End-study mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo qd	8	370.0 ± 8.9	371.3 ± 8.5	1.3 ± 7.7	
	Fexofenadine 60 mg qd	8	360.6 ± 8.9	368.8 ± 9.1	8.1 ± 10.2	0.5302
	Fexofenadine 120 mg qd	7	367.1 ± 8.1	361.4 ± 9.1	-5.7 ± 7.2	0.5390
	Fexofenadine 180 mg qd	10	372.0 ± 9.4	368.2 ± 7.4	-3.8 ± 5.0	0.6266
	Fexofenadine 240 mg qd	7	364.3 ± 8.7	368.6 ± 12.4	4.3 ± 8.4	0.7884

*P-value is from ANCOVA, active treatment vs. placebo. End-study=last visit for which information was available. Dose Response (linear trend)=0.8140. [1]n=a subset of patients from study 0019 (at study site #40 in France) who had ECGs performed.

Table XIII: Controlled Pediatric SAR Studies (0066/0077 Combined)
Mean QT_c Change from Baseline for Fexofenadine 15 mg, 30 mg, and 60 mg bid, compared to Placebo [V1.299:249]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	End-study mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo bid	221	407.9 ± 1.3	408.0 ± 1.6	0.15 ± 1.7	
	Fexofenadine 15 mg bid	218	405.9 ± 1.4	406.6 ± 1.4	0.75 ± 1.6	0.7906
	Fexofenadine 30 mg bid	206	405.2 ± 1.4	406.2 ± 1.5	0.99 ± 1.6	0.7167
	Fexofenadine 60 mg bid	210	406.2 ± 1.3	407.1 ± 1.5	0.88 ± 1.6	0.7496

*P-value is from ANCOVA, active treatment vs. placebo. End-study=last visit for which information was available. Dose Response (linear trend)=0.7379.

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Table XIV: Controlled Pediatric SAR Studies (0066/0077 Combined) Change from Baseline in QT, QRS, PR, and HR Means for Fexofenadine 15 mg, 30 mg, and 60 mg bid, compared to Placebo [V1.299:250]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	Endstudy mean ± SE	Change from Baseline mean ± SE	
QT (msec)	Placebo	221	354.8 ± 1.5	359.6 ± 1.7	4.81 ± 1.5	
	Fexofenadine 15 mg bid	218	355.2 ± 1.7	359.9 ± 1.7	4.62 ± 1.3	0.9243
	Fexofenadine 30 mg bid	206	355.1 ± 1.8	357.5 ± 1.9	2.33 ± 1.4	0.2124
	Fexofenadine 60 mg bid	210	351.0 ± 1.6	356.4 ± 1.7	5.42 ± 1.4	0.7563
QRS (msec)	Placebo	221	82.0 ± 0.4	81.5 ± 0.3	-0.52 ± 0.4	
	Fexofenadine 15 mg bid	218	82.6 ± 0.4	82.2 ± 0.4	-0.37 ± 0.3	0.7436
	Fexofenadine 30 mg bid	206	82.2 ± 0.3	82.0 ± 0.4	-0.22 ± 0.4	0.5323
	Fexofenadine 60 mg bid	210	82.1 ± 0.3	81.6 ± 0.4	-0.50 ± 0.3	0.1971
PR (msec)	Placebo	221	138.6 ± 1.0	140.0 ± 1.0	1.41 ± 0.8	
	Fexofenadine 15 mg bid	218	138.5 ± 1.1	138.9 ± 0.9	0.40 ± 0.8	0.3927
	Fexofenadine 30 mg bid	206	138.8 ± 1.0	139.0 ± 1.0	0.20 ± 0.9	0.3171
	Fexofenadine 60 mg bid	210	139.4 ± 1.1	139.3 ± 1.2	-0.14 ± 0.9	0.1971
HR (bpm)	Placebo	221	80.3 ± 0.8	78.4 ± 0.8	-1.87 ± 0.8	
	Fexofenadine 15 mg bid	218	79.5 ± 0.8	77.8 ± 0.8	-1.67 ± 0.8	0.8563
	Fexofenadine 30 mg bid	206	79.3 ± 0.8	79.0 ± 1.0	-0.36 ± 0.9	0.1745
	Fexofenadine 60 mg bid	210	81.3 ± 0.7	79.3 ± 0.8	-2.03 ± 0.7	0.8887

*P-value is from ANCOVA. Endstudy=last visit for which information was available.

Table XV: Controlled Pediatric SAR Studies (0066/0077 Combined) Mean QT_c Change from Baseline for Fexofenadine 15 mg, 30 mg, and 60 mg bid, compared to Placebo [V1.299:249]

ECG Parameter	Patients with QTc *Outlier Values (n/total, n%)			
	Placebo bid	Fexo 15 mg bid	Fexo 30 mg bid	Fexo 60 mg bid
QTc (msec)	7/221	6/218	6/206	3/210
	3.2%	2.8%	2.9%	1.4%

* QT_c interval outliers defined by pre-specified ECG criteria in the study protocol by the sponsor as a QT_c interval outlier > 450 msec with an increase > 10 msec [V1.225:130].

Table XVI: Study 0027: 1 Year Long-term Safety Study in Healthy Volunteers; Average Baseline, Endstudy and Change from Baseline ECG Parameter Values for Fexofenadine 240 mg po qd vs. Placebo [V1.259:89]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	Endstudy mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo	233	396.9 ± 1.47	402.5 ± 1.42	5.6 ± 1.49	0.1876
	Fexofenadine 240 mg	231	398.4 ± 1.44	401.4 ± 1.50	3.0 ± 1.32	
QT (msec)	Placebo	233	387.4 ± 1.54	388.2 ± 1.69	0.8 ± 1.42	0.7614
	Fexofenadine 240 mg	231	388.7 ± 1.73	390.1 ± 1.77	1.4 ± 1.39	
QRS (msec)	Placebo	233	81.5 ± 0.44	84.3 ± 0.52	2.7 ± 0.47	0.3150
	Fexofenadine 240 mg	231	80.8 ± 0.44	82.9 ± 0.43	2.1 ± 0.41	
PR (msec)	Placebo	233	149.3 ± 1.33	151.5 ± 1.26	2.3 ± 0.90	0.2931
	Fexofenadine 240 mg	231	147.8 ± 1.18	151.4 ± 1.23	3.6 ± 0.90	
HR (bpm)	Placebo	233	63.6 ± 0.60	65.3 ± 0.67	1.7 ± 0.64	0.1860
	Fexofenadine 240 mg	231	63.7 ± 0.61	64.3 ± 0.65	0.6 ± 0.57	

*P-value is from ANCOVA. Endstudy=last visit for which information was available.

Table XVII: Study 0027: 1 Year Long-term Safety Study in Healthy Volunteers Average Baseline and Maximum-Postbaseline ECG Values for Fexofenadine 240 mg po qd vs. Placebo [V1.259:90]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	Maximum mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo	233	396.9 ± 1.47	417.0 ± 1.28	20.1 ± 1.29	0.0357
	Fexofenadine 240 mg	231	398.4 ± 1.44	414.6 ± 1.33	16.2 ± 1.32	
QT (msec)	Placebo	233	387.4 ± 1.54	406.1 ± 1.66	18.7 ± 1.19	0.5745
	Fexofenadine 240 mg	231	388.7 ± 1.73	406.3 ± 1.68	17.6 ± 1.35	
QRS (msec)	Placebo	233	81.5 ± 0.44	87.7 ± 0.49	6.1 ± 0.40	0.1530
	Fexofenadine 240 mg	231	80.8 ± 0.44	86.2 ± 0.42	5.3 ± 0.38	
PR (msec)	Placebo	233	149.3 ± 1.33	161.9 ± 1.70	12.6 ± 1.24	0.5562
	Fexofenadine 240 mg	231	147.8 ± 1.18	159.5 ± 1.21	11.7 ± 0.84	
HR (bpm)	Placebo	233	63.6 ± 0.60	71.3 ± 0.70	7.8 ± 0.61	0.0247
	Fexofenadine 240 mg	231	63.7 ± 0.61	69.5 ± 0.68	5.8 ± 0.62	

*P-value from 2 sample test from maximum-baseline in ECG values between treatment groups.

10.10. Special Populations

None of the studies for NDA 20-872 were conducted in renally or hepatically impaired subjects, or elderly subjects over the age of 65 years, however, ALLEGRA 60 mg capsules were studied in hepatically and renally impaired patients and the elderly in NDA 20-625, with PK information obtained. Conclusions based on these studies indicated that despite the apparent differences in PK results in renally-impaired and elderly patients, use of fexofenadine HCl is considered safe in these groups. In hepatically-impaired patients, the PK of fexofenadine appeared to be independent of the severity of hepatic impairment

and comparable to those observed in healthy volunteers [V1.63:226]. PK information with respect to these 3 patient populations and dosing information with regard to renal impairment (no effect of hepatic impairment on PK) is provided in the current label for ALLEGRA 60 mg capsules and is proposed in the label for ALLEGRA tablets.

10.11. 120-Day Safety Update

Review of the sponsor's 120-Day Safety Update dated 11/10/98 for ALLEGRA lactose-free tablets indicated that 2 clinical pharmacology studies, 3 controlled clinical studies, and 25 post-marketing studies were ongoing or completed in this time period. Since many of these trials were only recently completed, study reports were not available for any of these trials.

No deaths were reported in these studies during this 9-month period. A total of 11 'serious' adverse events were reported: 6 AEs resulting in hospitalization, 1 overdose, and 4 AEs that met criteria for 'medical importance'. These AEs are summarized in S9.V1:31 but particularly relevant AEs included: (1) a report of a cardiac dysrhythmia (rapid heart rate) in a 63 yo female after taking the 1st dose of fexofenadine 120 mg (study C002, patient # 1585-0001), (2) syncope in a 23 yo female within 15 minutes at a disco that occurred ~ 3 days after 1 dose of fexofenadine 120 mg (study C002, patient # 1678-0003), (3) development of angina and decreased blood pressure in a 61 yo male taking fexofenadine 120 mg for 3 days who had a previous history of angina (study C002, patient # 2225-0003, and (4) a case of inadvertent overdose with 3, 120 mg tablets qd for 20 days in an 18 yo male that resulted in frequent headaches which resolved upon reduction of the medication dose to 120 mg qd (study C002, patient # 0224-0005) [S9.V1:233-249, 251-317, 318-337, 355-377].

In addition, in 1 of the clinical pharmacology studies (1104), 1 subject reported chest tightness on 2 occasions: the 1st event occurred 2 days after receiving 1 dose of fexofenadine 120 mg and last 9 days (into the 1st 2 days of the 2nd session) and the second event occurred 3.5 hours after treatment (terfenadine 60 mg) in the 3rd session and lasted 19.5 hours [S9.V1:20]. The symptom resolved spontaneously on both occasions and 12-lead ECG performed while the subject experienced chest tightness showed no abnormalities. Nonetheless, without any other clear explanation for these events, they were deemed to be 'possibly related' to study medication.

In summary, data from the 120-Day Safety Update supported the safety profile already delineated in NDA 20-872 (and previous NDA 20-625), as no new trends or safety concerns were identified in this follow-up report.

11.0. Data Verification (DSI Audit)

A Division of Scientific Investigations (DSI) audit of the clinical data for all of the pivotal studies submitted to this NDA (adult SAR study 3081, pediatric SAR study 0077, and CIU studies 0039 and 0067) was conducted as a prerequisite of NDA approval of ALLEGRA tablets since a new formulation was being

evaluated in 2 new patient populations or at a different dosing regimen (qd dosing).

At the time of submission of NDA 20-872, it was noted that one of the clinical investigators, Dr. Thomas Edwards, who served as a clinical investigator in 3 pivotal studies for each of the 3 clinical indications being evaluated in this NDA submission (adult qd SAR study 3081, pediatric SAR study 0066 and CIU study 0039), was placed on the disqualified investigator list. The sponsor of NDA 20-872 was informed of our concerns and submitted re-analysis of all primary efficacy data for the 3 pivotal studies in which Dr. Edwards had participated, having had excluded those study sites from efficacy analysis. Re-analysis of the primary efficacy data for these 3 studies failed to show a statistically significant difference in the primary efficacy endpoints. Furthermore, no significant difference in safety findings was seen when Dr. Edwards' sites were excluded.

An additional DSI issue raised at the 21-day filing meeting was the choice of studies and sites that would be audited as part of the data integrity check. The statistical reviewer for NDA 20-872—Ms. Barbara Elashoff, had noted that for the pediatric SAR study PJPR0077, in one of the study sites (#904, Dr. David F. Graft, 14 patients), patients demonstrated greater efficacy in terms of numerical change than other study sites, and it was thus determined that this particular site should be audited to determine the accuracy of data entry and transcription. However, study records at Dr. Graft's practice were damaged during the Texas floods of 1997 to the extent that despite drying the source documents, data were not legible. In concert with DSI, another study site was recommended for auditing, that of Dr. William E. Berger (pivotal adult SAR study 3081, 29 patients). Dr. H. W. Ju from the DSI Branch likewise recommended auditing site #900 (Dr. Thomas B. Casale, 18 patients) for study PJPR0077, as the investigator has been recently implicated in possible study misconduct. In addition to auditing a second pediatric SAR study, it was determined that the 2 adult CIU studies should be audited for quality control since the CIU indication is a new clinical indication for fexofenadine HCl. The study sites chosen for auditing were as follows: CIU study PJPR0039: site 296—Dr. Anjuli S. Nayak (IL, 28 patients) and CIU study PJPR0067: site 602—Dr. John J. Condemi (29 patients, NY).

For these pivotal trials, in addition to the routine parameters evaluated by DSI, primary efficacy endpoints were also be evaluated at baseline and after 2 and 4 weeks of treatment (for SAR and CIU, respectively), along with important inclusion criteria (such as confirmation that the patient had CIU for e.g.) for patient enrollment into the study.

Results of this audit revealed no significant discrepancies for most of the investigators, with 'no action indicated'. At Dr. William Berger's study site, a number of protocol violations were seen: (1) randomization of patients (#005, 010, and 012) who were not qualified for the study based on self-rated week 1 instantaneous symptom scores, (2) randomization of a patient into the study (#021) who received an intranasal corticosteroid 9 days prior to the first dose of the study medication, and (3) failure to maintain documentation of skin tests for

subjects #010 and 012. At Dr. Nayak's study site, a number of subjects did not have the revised protocol consent signed. For both of these investigators a 'voluntary action indicated' (VAI) report was issued. 'For cause' audit of Dr. Casale's study site failed to reveal any significant violations and report from the investigator indicated that patient records were kept in excellent order. Review of data for primary efficacy endpoints which were pre-specified by the medical officer prior to the audit revealed no discrepancies in the patients' diaries and the source documents. The only violations noted during this audit included: dating of a patient informed consent by the investigator on a day when the investigator was not in the office and dating of progress notes on several patients on days that the investigator was likewise not in the office (patients were seen those days by the study coordinator).

In summary, with the exception of Dr. Edwards' sites which were excluded from data analysis, no major protocol violations or discrepancies were seen during the DSI audit 4 individual study sites (1 individual site each for each pivotal study) from the 4 pivotal studies reviewed in NDA 20-872.

12.0. CONCLUSION: Executive Summary of Efficacy and Safety

Evaluation of the efficacy of ALLEGRA tablets was performed for 3 separate indications in this NDA submission, as proposed by the sponsor: (1) once daily treatment of adult nasal SAR symptoms [redacted] 180 mg qd), (2) twice daily treatment of pediatric nasal SAR symptoms (30 mg or 60 mg bid), and (3) twice daily treatment of adult (60 mg bid) and pediatric (30 mg [redacted] CIU symptoms. This NDA is unique in that in its labeling it combines indications and formulations from the original ALLEGRA capsule NDA (#20-625) with that of the current submission for ALLEGRA tablets (#20-872). Pediatric PK data was used in the support of clinical efficacy for both the SAR and CIU indications via extension of the Pediatric Rule. Hence, the sponsor plans to market fexofenadine 30 mg, 60 mg, 120 mg, and 180 mg tablets, in addition to 60 mg capsules.

For the adult qd SAR indication, 3 trials were reviewed in total (3081, 0032, and 0061), one of which was considered pivotal (3081). A total of 1889 patients were exposed to fexofenadine in these trials. Two of these 3 trials (3081, 0032) evaluated fexofenadine 120 mg and 180 mg doses. For both the end-of-dosing interval (defined as the change from baseline in the 8:00 a.m. instantaneous total symptom score (TSS)) and the change from baseline in the 24 hour reflective TSS, both the fexofenadine 120 mg and 180 mg qd doses demonstrated a statistically significantly greater improvement over the 2 week double-blind period than placebo, though a greater numerical decrease was seen with the fexofenadine 180 mg qd dose. End-of-dosing interval results in the pivotal adult SAR trial 3081 were likewise supported by population PK analysis using NONMEM, in which the 120 mg fexofenadine dose was likely to provide marginal plasma fexofenadine concentrations at the end-of-dosing interval. In the pivotal study 3081, onset of action was evaluated on a daily basis, using the change from baseline in the 8:00 a.m. instantaneous TSS, with both fexofenadine doses demonstrating onset of action by 24 hours, consistent with current labeling for ALLEGRA. Hence, the most appropriate once daily dose of fexofenadine appears to be either the 120 mg qd or 180 mg qd dose, with the 180 mg dose affording a somewhat greater decrease in symptoms.

The pediatric SAR studies consisted of 2 identical studies 0066 and 0077 which were combined by the sponsor into 1 large study in order to obtain adequate numbers of patients to maintain powering in the study which was not achievable in the separate studies due to poor patient enrollment. Statistical review of this pooling found the sponsor's methods and rationale for pooling the 2 pediatric studies was not appropriate from the data analysis perspective. The overall design of the pediatric SAR trials was similar to that of the adult SAR trials. A total of 646 patients were exposed to fexofenadine in these trials.

Review of efficacy for the end-of-dosing interval (the change from baseline in average daily 7:00 a.m. and 7:00 p.m. instantaneous TSS) and the change from baseline in the average 7:00 p.m. reflective TSS over the 2 week double-blind treatment period, only showed a statistically significant difference for all 3 fexofenadine doses tested: 15 mg bid, 30 mg bid, and 60 mg bid for study 0077

and not for study 0066 and the combination of studies 0066 and 0077. In these latter 2 studies, none of the fexofenadine doses (even the highest, at 60 mg bid) demonstrated greater efficacy than placebo. While a number of explanations were sought to explain this discrepancy in clinical response between the 2 identical pediatric studies, including the inherent difficulty of conducting pediatric SAR trials, a greater placebo response was seen in study 0066 which would have impacted efficacy for both this individual trial and combined trials 0066/0077, and also made pooling of these 2 studies inappropriate. Onset of action was likewise evaluated in the combined pediatric studies 0066/0077 on a daily basis, using change from baseline in the 7:00 p.m. reflective TSS, and a statistically significant difference compared to placebo was seen for the fexofenadine 15 mg bid and 60 mg bid doses after 24 hours of dosing, which did not appear to be maintained after this time point.

While the sponsor proposed fexofenadine 30 mg bid or 60 mg bid as appropriate doses for the treatment of pediatric SAR symptoms, choice of the fexofenadine 30 mg bid dose by the medical officer as a more appropriate dose from a clinical and PK standpoint, was based on lack of a significant dose response seen between the 30 mg and 60 mg doses of fexofenadine in children that could justify marketing a higher dose, a dose-by-patient weight correlation with respect to plasma fexofenadine levels was not demonstrated in the PK analyses, and the 60 mg dose of fexofenadine yielded a plasma AUC and C_{max} in children which was almost twice that seen in adults, whereas the fexofenadine 30 mg dose demonstrated plasma AUC and C_{max} in children which was approximately the same to being slightly higher than that seen in adults. In addition to review of clinical data from combined studies 0066 and 0077 and separate studies 0066 and 0077, the basis for extrapolation of efficacy for the pediatric population was also based on the Pediatric Rule under the supposition that the pathophysiology of SAR is similar in adults and children (which they are) and comparable plasma fexofenadine levels to those of adults (similar or somewhat higher levels) were shown in children age 7-11 years treated with a single dose of fexofenadine 30 mg [V1.63:209].

For the CIU indication, a total of 3 trials were evaluated in adult patients (0039, 0067, and 0019), the 1st two of which were pivotal and examined twice daily dosing of fexofenadine: 20 mg, 60 mg, 120 mg, and 240 mg bid vs. placebo for 4 weeks. One non-pivotal trial (0019) evaluated once daily (qd) dosing of fexofenadine (60 mg, 120 mg, and 240 mg). A total of 897 patients were exposed to fexofenadine in these trials. Review of the primary efficacy endpoint for the 2 pivotal studies (the change from baseline in the mean pruritus score (MPS)) revealed a statistically significantly greater improvement in pruritus for all 4 fexofenadine treatment groups compared to placebo, with the smallest numerical change from baseline evident in the 20 mg bid group. The end-of-dosing interval was not evaluated in these trials. Based on these findings and results of non-pivotal study 0019 which showed efficacy of fexofenadine at the 180 mg qd and 240 mg qd doses compared to placebo, the most appropriate dose of fexofenadine

for the treatment of adult CIU would appear to be either the 60 mg bid dose, given that the 120 mg bid and 240 mg bid doses, and the 180 mg qd and 240 mg qd doses did not afford a significantly greater improvement in these clinical parameters than did the 60 mg bid dose. Choice of the appropriate pediatric dose of fexofenadine for treatment of CIU as 30 mg bid by the medical reviewer was established by the Pediatric Rule since CIU is comparable in terms of pathophysiology, symptoms and treatment in both adults and children and since similar exposure to drug was shown in children age 7-11 years as that seen in adults in a pediatric PK study (study 0037) from which data obained was able to link adult with pediatric exposure [V1.63:284-289]. Hence, no specific clinical trials were performed in children for the CIU indication.

Analysis of efficacy by demographic factors (age, gender, race, etc.) via ANCOVA failed to reveal any significant influence or trend.

Analysis of clinical efficacy for the 3 clinical indications proposed in this NDA separately by week 1 and week 2, revealed that fexofenadine generally achieved a statistically significant reduction in many efficacy endpoints by week 1 of treatment but continued to provide a greater numerical reduction in the respective symptoms by week 2 of treatment. The greatest degree of change for most endpoints, however, appeared to occur by week 1 of treatment.

The safety database for ALLEGRA tablets consisted of 1886 safety evaluable patients in the 3 adult SAR trials (of which 959 received fexofenadine 120 mg and 491 received fexofenadine 180 mg), 646 safety evaluable patients in the 2 pediatric SAR trials (of which 224 received fexofenadine 15 mg bid, 209 received fexofenadine 30 mg bid, and 213 received fexofenadine 60 mg bid), and 884 safety evaluable patients in the 3 adult CIU trials (in which 187 received fexofenadine 20 mg bid, 186 received fexofenadine 60 mg bid, 171 received fexofenadine fexofenadine 120 mg bid, and 169 received fexofenadine 240 mg bid) [Table II, Integrated Summary of Safety]. The majority of patients studied for all 3 clinical indications were exposed to < 30 days of medication.

Overall, ALLEGRA tablets were found to be safe and well-tolerated given at doses of 30 mg and 60 mg twice a day, and 120 mg and 180 mg once a day (the proposed 'to-be-marketed' doses) and at higher daily doses of up to 240 mg twice a day. No significant serious adverse events occurred in patients treated with ALLEGRA tablets that could be clearly linked with medication use, and only one death was reported due to a self-inflicted gunshot wound which was not due to study medication. Similar to placebo treatment, headache was the most common adverse event, followed by upper respiratory infection, and pharyngitis for the adult population (SAR and CIU). Coughing, injury accident, and fever were the most common AEs in the pediatric population (SAR studies). No clinically significant trends in 12-lead ECG findings or laboratory abnormalities were demonstrable in fexofenadine treated patients and no obvious difference in outlier values was noted between the various treatment groups for both adult and pediatric populations, and in adults--even when fexofenadine was given for up to 1 year (in healthy volunteers) at a dose of 240 mg qd (no pediatric trials at these

doses). Physical findings tended to be related to the underlying disorder, i.e. either SAR or CIU.

In summary, ALLEGRA tablets appear to be safe and effective for the once daily treatment of symptoms of SAR (excluding nasal obstruction) in adults and adolescents ≥ 12 years of age at the recommended dose of 120 mg or 180 mg qd, twice daily treatment of symptoms of SAR in children age 6-11 years (excluding nasal obstruction) at the recommended dose of 30 mg bid, and treatment of CIU in adults and adolescents ≥ 12 years of age at a dose of 60 mg bid and at a dose of 30 mg bid in children age 6-11 years. As per the current label, the medical officer recommends adjustment of these doses, as appropriate, for renal insufficiency.

12.1. Reviewer Recommendation:

ALLEGRA lactose-free tablets are shown to be safe and effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) (excluding nasal obstruction) in adults ≥ 12 years of age (60 mg bid, 180 mg qd, and most likely 120 mg qd--although review of significant efficacy findings for the 120 mg dose, especially for the end-of-dosing interval, in a completely corrected study report for SAR trial 0032 would add greater credence to support for the 120 mg dose) and by extension of the Pediatric Rule in children age 6-11 years of age (30 mg bid). ALLEGRA tablets are also shown to be safe and effective for the treatment of symptoms of chronic idiopathic urticaria (CIU) in adults ≥ 12 years of age (60 mg bid) and by extension of the Pediatric Rule in children age 6-11 years of age (30 mg bid). Fexofenadine 60 mg capsules may be substituted for fexofenadine 60 mg tablets, as the 2 dosage formulations are comparable in terms of the plasma concentration of fexofenadine afforded by both. The medical reviewer of NDA 20-872 recommends approval of ALLEGRA lactose-free tablets, for these clinical indications.

13.0. Labeling Comments

The sponsor's proposed label for ALLEGRA tablets (with inclusion of the new proposed indications) was reviewed by the medical officer. Overall, few changes were made to the currently approved label, although the following comments were offered by the reviewing medical officer for label revision. (Note: all additions are marked in '**bold-type**' and all deletions are marked in 'strike-out'):

4.B.1 Proposed text of labeling

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

Proposed Labeling