CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-032/S-016 and S-017

Administrative Documents

RHPM Review of Final Printed Labeling
NDA 19-032/ S-016 and S-017

Date of Submission: October 31, 2001
Date of Review: March 1, 2002
Applicant Name: A. H. Robbins
Product Name: Tenex (guanfacine HCl) 1 and 2 mg Tablets

Evaluation:

These supplemental new drug applications provide for FPL with the following revisions to the labeling:

S-016

Added a **PRECAUTIONS/Geriatric Use** section

> Clinical studies of Tenex did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
>
> In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see **CLINICAL PHARMACOLOGY-Pharmacokinetics**).

S-017

Addition to the **PRECAUTIONS/Pediatric Use** section:

> There have been spontaneous postmarketing reports of mania and aggressive behavioral changes in pediatric patients with attention-deficit hyperactivity disorder (ADHD) receiving Tenex. The reported cases were from a single center. All patients have medical or family risk factors for bipolar disorder. All patients recovered upon discontinuation of guanfacine HCl.

The following minor editorial changes were noted:

- "Rx only" was added under the drug name on the first page of the package insert.
- "Tenex (guanfacine hydrochloride) Tablets are available in the following dosing strengths (expresses in equivalent amounts of guanfacine):" was added to the **How Supplied** section.
- Storage temperatures were change to "Store at controlled temperature, between 20°C and 25°C (68°F and 77°F)."
- Sponsor's code and revised dates were updated to reflect the most recent labeling changes.

In addition, the text in the **PRECAUTIONS/Pediatric Use** section was not identical to the text in the approvable letter dated February 23, 2001. At the time of the next printing, the sponsor will be requested to make the following correction to the **PRECAUTIONS/Pediatric Use** section in the package insert:

- In the next to the last sentence, change the word have to had.
- The sentence should read:

  All patients had medical or family risk factors for bipolar disorder.

Recommendation:

- An approval letter should be issued for these supplements with the addition of the revised text for the **PRECAUTIONS/Geriatric Use** and the **PRECAUTIONS/Pediatric Use** sections of the labeling as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

- The sponsor, at the time of the next printing, will be requested to correct the editorial error in the **PRECAUTIONS/Pediatric Use** section, as noted above, as noted above.

- The sponsor will be instructed to report the editorial revision in their next annual report.

/S/

Daryl Allis, RHPM

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/s/

Daryl L. Allis
3/11/02 01:57:16 PM
CSO

RHPM Review of Draft Labeling
NDA 19-032/S016

Date of Submission:	August 24, 2000
Date of Review:	February 9, 2001
Applicant Name:	A. H. Robbins
Product Name:	Tenex (guanfacine HCl) 1 and 2 mg Tablets

Evaluation:

This supplement provides for draft labeling revised by adding a Geriatric Use subsection to the **PRECAUTIONS/** sections:

> **Geriatric Use**
> Clinical studies of Tenex did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
>
> In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see **CLINICAL PHARMACOLOGY-Pharmacokinetics**).

In addition, the following minor text revisions were noted:

1. "Rx only" was added under the Tenex (Guanfacine Hydrochloride) Tablets text on the first page of the draft labeling.
2. The Sponsor code CI 4688-**3** and Revised **August 13, 1998** (bold Text) are struck out indicating proposed changes upon approval.

Recommendation:
An approvable letter should be issued for this supplement as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction] until Final Printed Labeling is submitted and approved.

/S/
Daryl Allis, RHPM

/s/

Daryl L. Allis
2/23/01 02:40:20 PM
CSO

RHPM Review of Final Printed Labeling
NDA 19-032/ S017

Date of Submission:	November 20, 2000
Date of Review:	February 9, 2001
Date Review Revised:	April 16, 2001
Applicant Name:	A. H. Robbins
Product Name:	Tenex (guanfacine HCl) 1 and 2 mg Tablets

Evaluation:

This is a Special Supplement- Changes Being Effected that provides for final printed labeling with the following revision to the **PRECAUTIONS/Pediatric Use** section of the labeling:

Added to the **Pediatric Use** section:

Draft

In addition, the Sponsor's code and revised dates were updated to reflect the most recent labeling changes.

This labeling supplement was discussed with Dr. Stockbridge regarding the postmarketing reports. A consult was sent to the Division of Drug Risk Evaluation I, HFD-430 on February 21, 2001.

Revision:

Consult from HFD-430 received on 4-9-01. Dr Stockbridge recommended the following changes to the **PRECAUTIONS/Pediatric Use** section of the labeling:

> "There have been spontaneous postmarketing reports of mania and aggressive behavioral changes in pediatric patients with attention-deficit hyperactivity disorder (ADHD) receiving Tenex. The reported cases were from a single center. All patients had medical or family risk factors for bipolar disorders. All patients recovered upon discontinuation of guanfacine HCl."

Recommendation:

This submission was sent in as a "Special Supplement-Changes Being Effected" for final printed labeling. The supplement is being processed as a prior approval.

An approvable letter should be issued for this supplement with the addition of the revised text for the **PRECAUTIONS/Pediatric Use** section of the labeling as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

/S/

Daryl Allis, RHPM

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/s/

Zelda McDonald
4/20/01 03:25:23 PM
CSO
For Daryl Allis

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Susan Lu, R.Ph., Postmarketing Safety Evaluator
Divison of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation I, HFD-430

TO: Raymond Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Postmarketing Safety Report (PID # D010091)
Drug : Tenex/Guanfacine - NDA# 19-032
Event(s): mania and aggressive behavioral changes

Contains data; not to be used outside of FDA without clearance by

EXECUTIVE SUMMARY

The evaluation of the reports of mania and aggressive behavioral changes in children with the use of guanfacine was prepared in response to a request dated 2/21/01 from the Division of Cardiorenal Drug Products. The sponsor has submitted a labeling supplement for adding a statement in the PRECAUTIONS/Pediatric Use section: "There have been spontaneous postmarketing reports of mania and aggressive behavioral changes in pediatric patients with attention-deficit hyperactivity disorder (ADHD) receiving Tenex." We have been requested to review the AERS database for these adverse reactions in children and to make recommendations regarding labeling changes.

A search was done in the Adverse Event Reporting System (AERS) database for any reports of mania and aggressive behavioral changes associated with guanfacine use. There were five unduplicated cases of mania in children with reasonable temporal relationship to monotherapy with guanfacine. These five patients, four males and one female, were part of a cohort of 95 children from a neuropsychiatric clinic who received guanfacine for the treatment of attention-deficit hyperactivity disorder. Four patients also had a diagnosis of Tourette's disorder. Each patient had been previously treated with other medications such as clonidine (4), methylphenidate (3), dextroamphetamine (3) and paroxetine (2). All patients either had a family history of mood disorders or had developed mania symptoms with previous exposure to antidepressants. In all cases, the symptoms of mania resolved quickly (within 24-72 hours) with discontinuation of guanfacine.

Aside from these five cases from the literature, there were no additional cases of mania or aggressive behavior associated with guanfacine in either adults or children. While these cases established good temporal relationship to guanfacine monotherapy with positive dechallenges, all patients were likely predisposed to mania by family or clinical history. If the division decides to approve the changes to the labeling proposed by the sponsor, we would recommend the following additional statements:

-

- Provide some information on this case series, for example, that - cases of mania in children from a single institution have been reported in the medical literature, that symptoms of mania resolved upon discontinuation of Tenex, and that all - patients had clinical and/or familial risk factors for bipolar disorder.

DRUG INFORMATION and LABELING

Guanfacine hydrochloride is a centrally acting alpha-2 agonist indicated in the management of hypertension, alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The use of guanfacine in children in the treatment of attention-deficit hyperactivity disorder is not approved by the agency.

The PRECAUTIONS section of the current product labeling contains the following information regarding the use of guanfacine in children:
Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Under ADVERSE REACTIONS section, Postmarketing Experience:
Psychiatric: agitation, anxiety, confusion, depression, insomnia, nervousness

DRUG USE

MEDICAL LITERATURE SUMMARY

A search of the medical literature on 3/20/01 using MEDLINE for information about mania and guanfacine produced two citations. These were two articles by Horrigan JP et al describing five cases of mania from a cohort of 95 children. These cases were reported to the AERS database and were summarized in this document.

SELECTION OF CASE SERIES

On 3/15/01, three searches of the AERS database with guanfacine listed as the suspect agent were performed. The first search was for all adverse events associated with guanfacine in pediatric patients (aged 0-17). There were 104 reports. The most frequently reported MEDDRA terms were sedation (11), condition aggravated (8), convulsion NOS (6), drug interaction NOS (6), hypotension (6), mania (6), accidental overdose (5), bradycardia (5), headache (5) and muscle twitching (4).

The second and third searches were specifically for reports of mania and aggression (using both MEDDRA terms, mood alterations with manic symptoms (HLT) and aggression (PT)) in adults and in the pediatric population, respectively. There were no reports in adults and eight reports in the 0-17 age group. There was one duplicate report and two reports were excluded. One described hypoglycemia in a child on concurrent propranolol, methylphenidate and guanfacine and the other report was of episodic anger

outbursts in a patient on Wellbutrin and Risperdal therapy (guanfacine discontinued prior event).

The five AERS remaining reports of mania and aggression originated from the medical literature: Horrigan J et al, Guanfacine and secondary mania in children, Journal of affective disorders Aug 1999; 54 (3); 309-314. These cases are summarized below.

SUMMARY OF 5 CASES

Demographics of the five cases of mania in the 0-17 age group and the narrative summaries of these cases follow:

Age:	range 8-15 years, mean 11 years
Gender:	Male—4, Female—1
Therapy duration:	range—3-6 days (n=4)
Daily dose:	1 mg/day (5)
Indication:	ADHD/Tourette's disorder—4, ADHD—1
Dechallenge:	positive—5
Rechallenge:	none
Outcome:	hospitalization—1
Source/location:	U.S—5
Report year:	1999—5
Report type:	15-day—4, periodic—1

AERS# 3309787, MFR# 8-98278-044A, 1998

An 8-year-old male with AHDH, Tourette's syndrome and anxiety disorder was started on guanfacine (0.5mg QD x 1 day, then 0.5 mg bid). Past medical history included an idiosyncratic reaction to imipramine (irritability, incessant talking and insomnia) which resolved after discontinuation of drug. He also had previous treatment with clonidine, dextroamphetamine and paroxetine with minimal improvement. Forty-eight hours after the guanfacine dose increase, he displayed hyperactivity, elevated speech tone and pressure, excessive irritability, poor frustration tolerance and insomnia. At 72 hours, he exhibited destructive behavior (biting people, destroying furniture) and was singing loudly. A mania rating scale score (obtained by phone) was 38. Guanfacine was discontinued and he improved to baseline (MRS score 13) within 72 hours. Family history included major depression in his mother and probable cyclothymia in his father.

AERS # 3309791, MFR# 8-98279-002Z, 1998

A 9-year-old male with ADHD, Tourette's disorder and developmental articulation disorder was started on guanfacine at a dose of 0.5 mg at bedtime for 2 days then increased to 0.5 mg bid on the third day. Past medication trials included methylphenidate, dextroamphetamine, clonidine, pimozide and amantadine with little improvement. A previous trial of fluoxetine resulted in hypomania (excessive irritability, pressured speech, hyperactivity, and physical aggression) which resolved within 2 weeks of drug

discontinuation. He continued to experience baseline hyperactivity, inattention and sporadic motor tics prompting a trial with guanfacine. He experienced increase in motor tics, incessant talking, agitation and aggressiveness while on guanfacine. Guanfacine was discontinued and his symptoms improved over the next 3 days. The Mania Rating Scales (completed by mother) showed a drop in score from 33 to 11 during those 3 days. A review of family history revealed three generations of affective disorders including a possible cyclical mood disorder in the father.

AERS# 3309793, MFR# 8-98279-003Z, 1998

An 11-year-old male with ADHD, Tourette's disorder and obsessive-compulsive disorder was started on guanfacine 0.5 mg daily for 2 days and increased to 0.5 mg bid on Day 3. Past medications trials resulting in undesirable side effects included methylphenidate (intense rebound symptoms especially irritability), dextroamphetaine (acute delirium and explosive aggression), paroxetine (psychomotor agitation) and clonidine (sedation). Initially, he had a good response on guanfacine but on Day 3, he developed insomnia, increased irritability and oppositionality. By Day 5, significant mood lability, pressured speech and frequent masturbation were occurring. Guanfacine was discontinued and he returned to baseline (MRS score from 31 to 12). Family history revealed a diagnosis of dysthmia in the mother.

AERS# 3356737, MFR# 8-99261-0161A, 1998

A 12-year-old male with ADHD and various developmental disorders received guanfacine (0.5 mg daily for 2 days then 0.5 mg bid) for impulsiveness, reactive aggression, inattention and distractability. Previous medication included methylphenidate (caused affective rebound), nortriptyline, bupropian, fluoxetine (caused incessant laughing and insomnia) and lithium. On day 4 of guanfacine use, there was an escalation in disruptive behavior, resulting in suspension from school. By day 5, he was hypertalkative, laughing incessantly and physically aggressive (pulled a knife on his mother). He was hospitalized on day 6 with a Mania Rating Scale score of 42. Guanfacine was discontinued, lorazepam was given and the MRS score dropped to 12. No family history was available because he was adopted.

AERS# 3309790, MFR# 8-98278-045A, 1998

A 15-year-old female with ADHD, Tourette's disorder and oppositional defiant disorder had been on clonidine monotherapy (0.2mg daily) for 2 years for tics and disruptive behavior. Due to rebound effects (irritability and increased motor tics), clonidine was tapered to 0.1mg daily, and she was then switched to guanfacine 0.5 mg bid. During the following three days, she became agitated with concurrent mental excitedness (pressured and voluminous speech), had deteriorating sleep hygiene and heightened interest in sexual themes. She became aggressive and assaulted her mother. Guanfacine was discontinued and clonidine was restarted. Within 72 hours, symptoms abated. Retrospective MRS scores dropped from 41 to 15. Family history included a bipolar disorder in her mother and intermittent explosive disorder and alcohol abuse in her father.

DISCUSSION AND CONCLUSION

These five patients, four males and one female aged 8 to 15, were part of a cohort of 95 children who received guanfacine as outpatients in a university-based neuropsychiatric outpatient clinic. Each received the same dosage regimen (1mg/day) for the treatment of ADHD and four children also had a diagnosis of Tourette's disorder. All five patients had received previous therapy with other medications, most commonly clonidine (4), methylphenidate (3), dextroamphetamine (3) and paroxetine (2). Four patients had experienced symptoms of mania associated with previous medication regimen. Each patient received guanfacine as monotherapy and with discontinuation of drug, symptoms of mania resolved relatively quickly (within 24-72 hours). Of note, all patients had either a family history of mood disorders (patient # 1,2,3,5) or had developed manic symptoms (patient # 1,2,4) with previous exposure to antidepressants. These cases suggest that guanfacine may precipitate mania in children with risk factors for mood disorders.

Other than the five cases described in the literature citation, there were no other AERS cases of mania or aggression in either children or adults.

The sponsor has proposed adding the following statement in the PRECAUTIONS/ Pediatric use section: "There have been spontaneous postmarketing reports of mania and aggressive behavioral changes in pediatric patients with attention-deficit hyperactivity disorder (ADHD) receiving Tenex". If the division decides to approve these changes to the labeling, we would make the following additional recommendations:

- Revise the current language in the PRECAUTIONS/Pediatric Use section to state that

- Provide some information on this case series, for example, that — cases of mania in children from a single institution have been reported in the medical literature, that - symptoms of mania resolved upon discontinuation of Tenex, and that all - patients had clinical and/or familial risk factors for bipolar disorder.

S

Susan Lu, Safety Evaluator

Concur:

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Claudia Karwoski, Team Leader

cc:

HFD-430/Beitz/Trontell/Karwoski/Lu/Guinn/Division file
HFD-400/Honig
HFD-110/Stockbridge/Allis/NDA# 19-032/Division file
HFD-120/Mosholder

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/s/

Claudia Karwoski
4/9/01 03:39:33 PM
PHARMACIST
for Susan Lu, R.Ph.

Julie Beitz
4/9/01 03:56:55 PM
DIRECTOR