Rev. 10/19

EXTENDED-RELEASE TABLETS, for oral use

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GUANFACINE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for GUANFACINE EXTENDED-RELEASE TABLETS.

GUANFACINE extended-release tablets, for oral use

### Initial U.S. Approval: 1986

---- INDICATIONS AND USAGE --Guanfacine extended-release tablets are central alpha<sub>2A</sub>-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications (1, 14).

- ---- DOSAGE AND ADMINISTRATION -• Recommended dose: 1 mg to 7 mg (0.05-0.12 mg/kg target weight based dose range) once
- daily in the morning or evening based on clinical response and tolerability (2.2). • Begin at a dose of 1 mg once daily and adjust in increments of no more than 1 mg/week (2.2).
- Do not crush, chew or break tablets before swallowing (2.1).

FULL PRESCRIBING INFORMATION: CONTENTS\*

DOSAGE AND ADMINISTRATION

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FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

Weight

25 to 33.9 kg

34 to 41.4 kg

49.5 to 58.4 kg

58.5 to 91 kg

>91 kg

following above recommended schedule

harmacology (12.3)].

2.4 Maintenance Treatme

evaluated in adolescents (ages 13 to 17 years)

5.3 Cardiac Conduction Abnormalities

5.1 Hypotension, Bradycardia, and Syncope5.2 Sedation and Somnolence

2.6 Missed Doses

- Do not administer with high-fat meals, because of increased exposure (2.1)
- Do not substitute for immediate-release quanfacine tablets on a ma-per-ma basis, because of differing pharmacokinetic profiles (2.3).
- If switching from immediate-release guanfacine, discontinue that treatment and titrate with guanfacine extended-release tablets as directed (2.3).
- When discontinuing, taper the dose in decrements of no more than 1 mg every 3 to 7 days to avoid rebound hypertension (2.5).

### ----- DOSAGE FORMS AND STRENGTHS Extended-release tablets: 1 mg, 2 mg, 3 mg and 4 mg (3)

-- CONTRAINDICATIONS History of hypersensitivity to guanfacine extended-release tablets, its inactive ingredients, or

other products containing guanfacine (4). - WARNINGS AND PRECAUTIONS -Hypotension, bradycardia, syncope: Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease or chronic renal failure. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while

Switching from Immediate-Release Guanfacine to Guanfacine Extended-Release Tablets

Guanfacine extended-release tablets are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications [see CLINICAL STUDIES (14)].

2.1 General Instruction for Use
Swallow tablets whole. Do not crush, chew, or break tablets because this will increase the rate of guanfacine release. Do not

In monotherapy clinical trials, there was dose- and exposure-related clinical improvement as well as risks for several clinically

Doses above 4 mg/day have not been evaluated in children (ages 6 to 12 years) and doses above 7 mg/day have not beei

In the adjunctive trial which evaluated guanfacine extended-release tablets treatment with psychostimulants, the majority o patients reached optimal doses in the 0.05 to 0.12 mg/kg/day range. Doses above 4 mg/day have not been studied in

Do not substitute for immediate-release avanfacine tablets on a milliaram-per-milliaram basis, because of differing

If switching from immediate-release guanfacine, discontinue that treatment, and titrate with guanfacine extended-release tablets

harmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate

the long-term use of guanfacine extended-release tablets, and adjust weight-based dosage as needed. The majority of children

and adolescents reach optimal doses in the 0.05 to 0.12 mg/kg/day range. Doses above 4 mg/day have not been evaluated in children (ages 6 to 12 years) and above 7 mg/day have not been evaluated in adolescents (ages 13 to 17 years) [see CLINICAL STUDIES (14)].

2.3 Switching from Immediate-Release Guanfacine to Guanfacine Extended-Release Tablets

ianificant adverse reactions (hypotension, bradycardia, sedative events). To balance the exposure-related potential benefits and rgament warest extensions (trypositiston), analyse and, security evens), I coulone the expositional better this kisk, the recommended target dose range depending on clinical response and tolerability for guanfacine extended-telease ablets is 0.05 to 0.12 mg/kg/day (total daily dose between 1 to 7 mg) (See **Table 1**).

each day. Begin at a dose of 1 mg/day, and adjust in increments of no more than 1 mg/week

Table 1: Recommended Target Dose Range for Therapy with Guanfacine Ex

ease tablets orally once daily, either in the morning or evening, at approximately the same time

Target dose range (0.05 to 0.12 mg/kg/dgv)

2 to 3 mg/day

2 to 4 mg/day

3 to 5 mg/day

4 to 7 mg/day

5 to 7 mg/day

2.7 Dosage Adjustment with Concomitant Use of Strong and Moderate CYP3A4 10 OVERDOSAGE

on therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated.

Advise patients to avoid becoming dehydrated or overheated (5.1).

Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to guanfacine extended-release tablets (5.2). Cardiac Conduction Abnormalities: May worsen sinus node dysfunction and atrioventricular

Sedation and somnolence: Occur commonly with quantacine extended-release tablets.

(AV) block, especially in patients taking other sympatholytic drugs. Titrate slowly and onitor vital signs frequently (5.3).

Rebound Hypertension: Abrupt discontinuation of guanfacine extended-release tablets can lead to clinically significant and persistent rebound hypertension. Subsequent hypertensive encephalopathy was also reported. To minimize the risk of rebound hypertension upon discontinuation, the total daily dose of quanfacine extended-release tablets should be tapered in decrements of no more than 1 mg every 3 to 7 days (5.4).

# ----- ADVERSE REACTIONS ---

Most common adverse reactions (≥5% and at least twice placebo rate) in fixed-dose monotherapy ADHD trials in children and adolescents (6 to 17 years): hypotension, somno fatique, nausea, and lethargy (6.1).

Flexible dose-optimization ADHD trials in children (6 to 12 years) and adolescents (13 to 17 years): someolence, hypotension, abdominal pain, insomnia, fatigue, dizziness, dry mouth, irritability, nausea, vomiting, and bradycardia (6.1). Adjunctive treatment to psychostimulant ADHD trial in children and adolescents (6 to 17 years):

omnolence, fatigue, insomnia, dizziness, and abdominal pain (6.1). To report SUSPECTED ADVERSE REACTIONS, contact TWI Pharmaceuticals, In 1-844-518-2989 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- ---- DRUG INTERACTIONS -• Strong and moderate CYP3A4 inhibitors increase guanfacine exposure. Decrease guanfacine extended-release tablets to 50% of target dosage when coadministered with strong and
- moderate CYP3A4 inhibitors (2.7). Strong and moderate CYP3A4 inducers decrease quanfacine exposure. Based on patient response, consider titrating guanfacine extended-release tablets dosage up to double the target dosage over 1 to 2 weeks (2.7)

7 DRUG INTERACTIONS

8.4 Pediatric Use

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2.5 Discontinuation of Treatment

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CYP3A4 Strong and

3 DOSAGE FORMS AND STRENGTHS

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension, Bradycardia, and Syncope

4 CONTRAINDICATIONS

pharmacokinetic profiles. Guanfacine extended-release tablets have significantly reduced C<sub>max</sub> (60% lover), biovairely, and a delayed T<sub>max</sub> (3 hours later) compared to those of the same dose of immediate-release guanfacine [see Clinical

1 mg 2 mg 3 mg gnd 4 mg extended-release tablets

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES

\* Sections or subsections omitted from the full prescribing information are not listed.

returning accommonant a Quantitaties according to the Control See Marinings and Precautions (5.4) and Adverse Reactions (6)]. Patients/carregivers should be instructed not to discontinue guantacine extended-release tablets without consulting their health care provider. Monitor blood pressure and pulse when reducing the dose or discontinuing the drug. Toper the daily dose in decrements of no more than 1 mg every 3 to 7 days to

When reinitiating patients to the previous maintenance dose after two or more missed consecutive doses, consider titration base

Dosage adjustments for guanfacine extended-release tablets are recommended with concomitant use of strong and moderate CYP3A4 inhibitors (e.g., ketoconazole), or CYP3A4 inducers (e.g., carbamazepine) (Table 2) [see DRUG INTERACTIONS

Table 2: Guanfacine Extended-Release Tablets Dosage Adjustments for Patients Taking Concomitant

CYP3A4 Inhibitors or Inducers

Clinical Scenario

Continuing guanfacine

extended-release tablets dosage to half the

(see Table 1)

Consider increasing

mmended level.

the recommended level over level over 1 to 2 weeks.

1 to 2 weeks. (see Table 1) (see Table 1)

dosage to recommende

level. (see Table 1)

2.7 Dosage Adjustment with Concomitant Use of Strong and Moderate CYP3A4 Inhibitors or Inc

dosage to half the

(see Table 1)

ended level.

ended level. (see Table 1)

Guanfacine extended-release tablets are contraindicated in patients with a history of a hypersensitivity reaction to guanfacine

Treatment with avanfacine extended-release tablets can cause dose-dependent decreases in blood pressure and heart rate.

Decreases were less pronounced over time of treatment. Orthostatic hypotension and syncope have been reported [see Adverse

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therap

Consider increasing

16 HOW SUPPLIED/STORAGE AND HANDLING

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See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 10/19

that may be worsened by hypotension and bradycardia; e.g., heart block, bradycardia, cardiovascular disease, vascular disease, Monotherapy Flexible Dose Trials cerebrovascular disease, or chronic renal failure. In patients who have a history of syncope or may have a condition that redisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration, advise patients to avoid ecoming dehydrated or overheated. Monitor blood pressure and heart rate, and adjust dosages accordingly in patients treated oncomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope.

5.2 Sedation and Somnolence

5.2. Securior and sedation were commonly reported adverse reactions in clinical studies [see Adverse Reactions (6.1)]. Be using guantiacine extended-release tablets with other centrally active depressants, consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with uanfacine extended-release tablets. Advise patients to avoid use with alcoho

# 5.3 Cardiac Conduction Abnormalities

The sympatholytic action of augustacine extended-release tablets may worsen sinus node dysfunction and atrioventricular (AV) The symponicytic action to groundcare exeminest energies along may wrosen shall note depositation and antiverintrious (Ary) block, especially in patients taking other sympotholytic drugs. Thrate guardracine extended-releases tables slowly and monitor vital signs frequently in patients with cardiac conduction abnormalities or patients concomitantly treated with other sympotholyti

In post marketing experience, abrupt discontinuation of quanfacine extended-release tablets has resulted in clinically significant and persistent rehound hypertension above baseline levels and increases in heart rate. Hypertensive encentral and the also reported in association with rehound hypertension with both quantarine extended-release tablets and immediate relea guanfacine [see Adverse Reactions (6.2)]. In these cases, high-dosage guanfacine was discontinued; concomitant stimula use was also reported, which may potentially increase hypertensive response upon abrupt discontinuation of guanfacine.

Children commonly have gastrointestinal illnesses that lead to vomiting, and a resulting inability to take medications, so they may be especially at risk for rebound hypertension.

To minimize the risk of rebound hypertension upon discontinuation, the total daily dose of quanfacine extended-release tablet should be topered in decrements of no more than 1 mg every 3 to 7 days (see **Dosage and Administration** (2.51). Blood pressure and heart rate should be monitored when reducing the dose or discontinuing guanfacine extended-release tablets. If abrupt discontinuation occurs (especially with concomitant stimulant use), patients should be closely followed for rebound

### 6 ADVERSE REACTIONS

- The following serious adverse reactions are described elsewhere in the labeling:

  Hypotension, bradycardia, and syncope [see Warnings and Precautions (5.1)]
- Sedation and somnolence [see Warnings and Precautions (5.2)]
   Cardiac conduction abnormalities [see Warnings and Precautions (5.3)]
   Rebound Hypertension [see Warnings and Precautions (5.4)]
- To report SUSPECTED ADVERSE REACTIONS, contact TWi Pharmaceuticals, Inc. 1-844-518-2989 or FDA at

## 6.1 Clinical Trials Experience

Recause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a The data described below reflect clinical trial exposure to quantarine extended release tablets in 2 825 nations. This includes patients from completed studies in children and adolescents, ages 6 to 17 years and 495 patients in completed studies in

Fixed Dose Trials

# Table 3: Percentage of Patients Experiencing Most Common (≥ 5% and at least twice the rate for placebo) Adverse Reactions in Fixed Dose Studies 1 and 2

		Guanfacine Extended-Release Tablets (mg)				
Adverse Reaction Term	Placebo (N=149)	1mg* (N=61)	2mg (N=150)	3mg (N=151)	4mg (N=151)	All Doses of guanfacine extended-release tablets (N=513)
Somnolence a	11%	28%	30%	38%	51%	38%
Fatigue	3%	10%	13%	17%	15%	14%
Hypotension b	3%	8%	5%	7%	8%	7%
Dizziness	4%	5%	3%	7%	10%	6%
Lethargy	3%	2%	3%	8%	7%	6%
Nausea	2%	7%	5%	5%	6%	6%
Dry mouth	1%	0%	1%	6%	7%	4%

\* The lowest dose of 1 ma used in Study 2 was not randomized to patients weighing more than 50 kg. The somnolence term includes somnolence, sedation, and hypersomnia.
The hypotension term includes hypotension, diastolic hypotension, orthostatic hyp

pressure diastolic decreased, blood pressure systolic decreased).

# Table 4: Adverse Reactions Leading to Discontinuation (≥ 2% for all doses of guanfac extended-release tablets and > rate in placebo) in Fixed Dose Studies 1 and 2

			Guai	ıfacine Exte	nded-Releas	e Tablets (mg)
Adverse Reaction Term	Placebo (N=149)	1 mg* (N=61)	2 mg (N=150)	3 mg (N=151)	4 mg (N=151)	All Doses of guanfacine extended-release tablets (N=513)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
otal patients	4 (3%)	2 (3%)	10 (7%)	15 (10%)	27 (18%)	54 (11%)
Somnolence a	1 (1%)	2 (3%)	5 (3%)	6 (4%)	17 (11%)	30 (6%)
atigue	0 (0%)	0 (0%)	2 (1%)	2 (1%)	4 (3%)	8 (2%)
Adverse reactions le	ndina to discon	tinuation in ≥	2% in any d	ose aroup bu	t did not meet	this criteria in all doses combined:

reased, blood pressure systolic decreased), headache, and dizziness. \*The lowest dose of 1 mg used in Study 2 was not randomized to patients weighing more than 50 kg.

# The compolence term includes somnolence, sedation, and hypersomnic

Table 5: Othe					es of gvantac Studies 1 an	ine extended-release tablets d 2
			Guai	ıfacine Exte	nded-Release	Tablets (mg)
Adverse Reaction Term	Placebo (N=149)	1 mg* (N=61)	2 mg (N=150)	3 mg (N=151)	4 mg (N=151)	All Doses of guanfacine extended-release tablets (N=513)
Headache	19%	26%	25%	16%	28%	23%
Abdominal Pain a	9%	10%	7%	11%	15%	11%
Decreased Appetite	4%	5%	4%	9%	6%	6%
Irritability	4%	5%	8%	3%	7%	6%
Constipation	1%	2%	2%	3%	4%	3%
Nightmare <sup>b</sup>	0%	0%	0%	3%	4%	2%
Enuresis <sup>c</sup>	1%	0%	1%	3%	2%	2%
Affect Lability d	1%	2%	1%	3%	1%	2%
						placebo in any dose group but did insomnia, terminal insomnia, sleep

sorder) vomiting diarrhen abdominal/stomach discomfort (abdominal discomfort enjanstric discomfort stomac assoraery, vomning, attermed, abbominal stomach assoraery (abbominal disconfort, epigestric assomator), stomach discomfort, post, forsh, rash generalized, rash popular), dyspepsia, increased weight, bradycardia (bradycardia, sinus bradycardia), asthma (asthma, branchospasm, wheezing), agitation, anxiety (anxiety, nervousness), sinus arrhythmia, blood ssure increased (blood pressure increased, blood pressure diastolic increased), and first dearee atrioventricular block

The lowest dose of 1 mg used in Study 2 was not randomized to patients weighing more than 50 kg. E. The abdominal pain term includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tend

b: The nightmare term includes abnormal dreams, nightmare, and sleep terror

		Guanfacine Extended-Release Tablets				
Adverse Reaction Term	Placebo (N=112)	AM (N=107)	PM (N=114)	All Doses of guanfacine extended-release tablets (N=221)		
Somnolence a	15%	57%	54%	56%		
Abdominal Pain <sup>b</sup>	7%	8%	19%	14%		
Fatigue	3%	10%	11%	11%		
Irritability	3%	7%	7%	7%		
Nausea	1%	6%	5%	5%		
Dizziness	3%	6%	4%	5%		
Vomiting	2%	7%	4%	5%		
Hypotension <sup>c</sup>	0%	6%	4%	5%		
Decreased Appetite	3%	6%	3%	4%		
Enuresis d	1%	2%	5%	4%		

Table 6: Percentage of Patients Experiencing Most Common (≥ 5% and at least twice the rate fo placebo) Adverse Reactions in the Monotherapy Flexible Dose Study 4

a: The somnolence term includes somnolence, sedation, and hypersomnia. The abdominal pain term includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tende

# Table 7: Adverse Reactions Leading to Discontinuation (≥ 2% for all doses of guan

		Guar	ıfacine Extended-	Release Tablets
Adverse Reaction Term	Placebo (N=112)	AM (N=107)	PM (N=114)	All Doses of guanfacine extended-release tablets (N=221)
	n (%)	n (%)	n (%)	n (%)
Total patients	0 (0%)	8 (7%)	7 (6%)	15 (7%)
Somnolence a	0 (0%)	4 (4%)	3 (3%)	7 (3%)
Adverse reactions leading to dis	continuation in ≥ 2%	in any dose group	but did not meet thi	s criteria in all doses combined:

a: The somnolence term includes somnolence, sedation, and hypersomn

The enuresis term includes enuresis, nocturia, and urinary incontin

# Table 8: Other Common Adverse Reactions (> 2% for all doses of augustacin

		Guanfacine Extended-Release Tablets			
Adverse Reaction Term	Placebo (N=112)	AM (N=107)	PM (N=114)	All Doses of guanfacine extended-release tablets (N=221)	
Headache	11%	18%	16%	17%	
Insomnia a	6%	8%	6%	7%	
Diarrhea	4%	4%	6%	5%	
Lethargy	0%	4%	3%	3%	
Constipation	2%	2%	4%	3%	
Dry Mouth	1%	3%	3%	3%	

not meet this criteria in all doses combined; affect lability (affect lability, mood swings), increased weight, syncope/loss o ciousness (loss of consciousness, presyncope, syncope), dyspepsia, tachycardia (tachycardia, sinus tachycardia), and

# Table 9: Percentage of Patients Experiencing Most Common (≥ 5% and at least twice the rate for placebo) Adverse Reactions in the Monotherapy Flexible Dose Study 5

dverse Reaction Term	Placebo (N=155)	All Doses of guanfacine extended-release tablets (N=157)
omnolence a	23%	54%
isomnia b	6%	13%
ypotension <sup>c</sup>	3%	9%
ry Mouth	0%	8%
ostural Dizziness	2%	5%
radycardia <sup>d</sup>	0%	5%
The samualence term includes so	mnolence sedution and hypersomi	nia

b: The insomnic form includes isomnice, including insomnic, middle insomnic, terminal insomnia, and sleep disorder

The hypotension term includes insomnic, midtle insomnic, middle insomnic, terminal insomnia, and sleep disorder

The hypotension term includes hypotension, diastolic hypotension, orthostatic hypotension, blood pressure decre pressure diastolic decreased, blood pressure systolic decreased). d: The bradycardia term includes bradycardia and sinus bradycardia

here were no specific adverse reactions  $\geq 2\%$  in any treatment group that led to discontinuation in the monotherapy flexible

		Guanfacine Extended-Release Tablets	
Adverse Reaction Term	Placebo (N=155)	All Doses of guanfacine extended-release tablets (N=157)	
Headache	18%	27%	
Fatigue	12%	22%	
Dizziness	10%	16%	
Decreased Appetite	14%	15%	
Abdominal Pain a	8%	12%	
Irritability	4%	7%	
Anxiety b	3%	5%	
Rash c	1%	3%	
Constipation	0%	3%	
Increased Weight	2%	3%	
Abdominal/Stomach Discomfort d	1%	2%	

Adverse reactions ≥ 2% for all doses of guanfacine extended-release tablets and > rate in placebo in any dose group but did not meet this criteria in all doses combined: nausea, diarrhea, vomitina, and depression (depressed mood, depression lepressive symptom). • The abdominal pain term includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tendernes:

: The rash term includes rash, rash generalized, and rash papular

Psychiatric confusion hallucination Reproductive System, Male: erectile dysfuncti

Adjunctive Trial

### age of Patients Experiencing Most Common (≥ 5% and at least twice the rate for placebo) Adverse Reactions in the Short-Term Adjunctive Study 3 Guanfacine Extended-Release Tablets + stimulant (N=150) (N=152) 18% 18% 6% 10% 14% 12% 8% 12% 12% 7%

7% 8%

3% 7%

3% a: The somnolence term includes somnolence, sedation, and hypersomnia. b: The insumnia term includes insumnia initial insumnia middle insumnia terminal insumnia and sleen disorder

There were no specific adverse reactions  $\geq 2\%$  in any treatment group that led to discontinuation in the short-term adjunctive

### Table 12: Other Common Adverse Reactions (≥ 2% for all doses of guanfacine extended-release tablets and > rate in placebo) in the Short-Term Adjunctive Study 3

		Guanfac	Guanfacine Extended-Release Tablets + stimulant			
Adverse Reaction Term	Placebo (N=153)	AM (N=150)	PM (N=152)	All Doses of Guanfacine Extended-Release Tablets (N=302)		
Headache	13%	21%	21%	21%		
Diarrhea	1%	4%	3%	4%		
Hypotensiona	0%	4%	2%	3%		
Constipation	0%	2%	3%	2%		
Affect Lability <sup>b</sup>	1%	3%	2%	2%		
Dry Mouth	0%	1%	3%	2%		
Bradycardia <sup>c</sup>	0%	1%	3%	2%		
Postural Dizziness	0%	1%	3%	2%		
Rashd	1%	1%	2%	2%		
Nightmaree	1%	2%	1%	2%		
Tachvcardia <sup>f</sup>	1%	2%	1%	2%		

Adverse reactions ≥ 2% for all doses of avanfacine extended-release tablets and > rate in placebo in any dose aroup but did not meet this criteria in all doses combined: irritability, vomiting, asthma (asthma, branchospasm, wheezing), and enuresis (enuresis, nocturia, urinary incontinence).

a: The hypotension term includes hypotension, diastolic hypotension, orthostatic hypotension, blood pressure decreased, blood

pressure diastolic decreased, blood pressure systolic decreased b: The affect lability term includes affect lability and mood swings

c: The bradycardia term includes bradycardia and sinus bradycard d: The rash term includes rash, rash generalized, and rash papula

The nightmare term includes abnormal dreams, nightmare, and sleep terror

f: The tachycardia term includes tachycardia and sinus tachycardia.

Effects on Blood Pressure and Heart Rate
In the monotherapy pediatric, short-term, controlled trials (Studies 1 and 2), the maximum mean changes from baseline in seated systolic blood pressure, diastolic blood pressure, and pulse were -5.4 mmHg, -3.4 mmHg, and -5.5 bpm, respectively, for all doses combined (generally one week after reaching target doses). For the respective fixed doses 1 mg/day, 2 mg/day, 3 mg/day or 4 mg/day the maximum mean changes in seated systolic blood pressure were -4.3 mmHg, -5.5 mmHg, -5.4 mmHg o my duy of a my duy me miximum internal manages in seatest system around resistance manage. 3.3 mining in 3.4 mining manages of the service of the maximum mean changes in seated and service of the maximum mean changes in seated of the service of the maximum mean changes in seated of the service of the maximum mean changes in seated of the service of the service of the maximum mean changes in seated of the service of the s pulse were -4.8 bpm, -3.1 bpm, -6.5 bpm and -8.6 bpm. Decreases in blood pressure and heart rate were usually modest and asymptomatic, however, hypotension and bradycardia can occur. Hypotension was reported as an adverse reaction for 7% of the guanfacine extended-release tablets group and 3% of the placebo group. This includes orthostatic hypotension, which was reported for 1% of the guanfacine extended-release tablets group and none in the placebo group. These findings were generally similar in the monotherapy flexible dose trials (Studies 4 and 5). In the adjunctive trial, hypotension (3%) and bradycardia (2%) were observed in patients treated with guanfacine extended-release tablets as compared to none in the placebo group. In long-term, open label studies, (mean exposure of approximately 10 months), maximum decreases in systolic and diastolic blood re occurred in the first month of therapy. Decreases were less pronounced over time. Syncope occurred in 1% of pediatri patients in the clinical program. The majority of these cases occurred in the long-term, open-label studie

Discontinuation of Treatment

Blood pressure and pulse may increase above baseline values following discontinuation of guanfacine extended-release tablets.

In five studies of children and adolescents [see CLINICAL STUDIES [14]], increases in mean systalic page of instance of the control of pressure averaging approximately 3 mmHg and increases in heart rate averaging 5 beats per minute above original baseline were observed upon discontinuation with tapering of guanfacine extended-release tablets. In a maintenance of efficacy study, reases in blood pressure and heart rate above baseline slowly diminished over the follow up period, which ranged bety and 26 weeks part in local pressure unin return tree under upsared to the pressure under the stimulated under the stands of the may have larger increases than reflected by the mean changes.

In postmarketing experience, following abrupt discontinuation of guardacine extended-release tablets, rebound hypertension an hypertensive encephalopathy have been reported [see Warnings and Precautions (5.4) and Adverse Reactions (6.2)]. Fletets on Height, Weight, and Body Mass Index (BMI)
Patients taking guanfacine extended-release tablets demonstrated similar growth compared to normative data. Patients taking guanfacine extended-release tablets had a mean increase in weight of 0.5 kg compared to those receiving placebo over a

youndurie exercises routes had a mean increase in regular to 2-xg compared to reserving processor exercises of comparable treatment period. Pallents receiving youndrine extended-release tablets for at least 12 months in open-label studies gained an average of 8 kg in weight and 8 cm (3 in) in height. The height, weight, and BMI percentile remained stable in Other Adverse Reactions Observed in Clinical Studies
Table 13 includes additional adverse reactions observed in short-term, placebo-controlled and long-term, open-label clinical

Table 13: Other adverse reactions observed in clinical studies				
Body System Adverse Reaction				
Cardiac	Atrioventricular block			
General	Asthenia, chest pain			
Immune System Disorders	Hypersensitivity			
Investigations	Increased alanine amino transferase			
Nervous system	Convulsion			
Renal	Increased urinary frequency			
Vascular	Hypertension, pallor			

reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Less frequent, possibly guanfacine-related events observed in the post-marketing study and/or reported spontaneously, not

General: edema, malaise, tremor Cardiovascular: palpitations, tachycardia, rebound hypertension, hypertensive encephalogathy Central Nervous System: paresthesias, vertigo

Eve Disorders: blurred vision Musculo-Skeletal System: arthralgia, leg cramps, leg pain, myalgia

# • Do not drive, operate heavy machinery, or do other dangerous activities until you know how

your thinking and motor skills.

# **Rev. 12**

# Read the Patient Information that comes with guanfacine extended-release tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment. What are avanfacine extended-release tablets?

Guanfacine extended-release tablets are prescription medicine used to treat the symptoms of attention deficit hyperactivity disorder (ADHD). Guanfacine extended-release tablets may be used alone or with ADHD stimulant medicines.

Guanfacine extended-release tablets are not central nervous system (CNS) stimulant.

It is not known if quanfacine extended-release tablets are safe and effective in children younger than 6 years of age.

# Who should not take guanfacine extended-release tablets?

Do not take avanfacine extended-release tablets if you are alleraic to avanfacine or any of the ingredients in quanfacine extended-release tablets. See the end of this leaflet for a complete list of ingredients in augnfacine extended-release tablets.

- have heart problems or a low heart rate
- have fainted
- have low or high blood pressure
- have liver or kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if guanfacine extended-release tablets will harm your unborn baby. Talk to your doctor if you are preanant or plan to become
- are breastfeeding or plan to breastfeed. It is not known if guanfacine extended-release tablets pass into your breast milk. Talk to your doctor about the best way to feed your baby while taking guanfacine extended-release tablets.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Guanfacine extended-release tablets may affect the way other medicines work, and other medicines may affect how guanfacine extended-release tablets work.

Especially tell your doctor if you take:

- ketocongzole
- medicines that can affect enzyme metabolism
- high blood pressure medicine
- sedutives
- henzodiazenines barbiturates
- antinsychotics

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when vou aet a new medicine.

# How should I take guanfacine extended-release tablets?

- Take quanfacine extended-release tablets exactly as your doctor tells you. • Your doctor may change your dose. Do not change your dose of guanfacine extended-release
- tablets without talking to your doctor. • Do not stop taking guanfacine extended-release tablets without talking to your doctor. • Try not to miss your dose of guanfacine extended-release tablets. If you miss a dose of
- guanfacine extended-release tablets, take the next dose at your regular time. If you miss 2 or
- more doses, talk to your doctor, as you may need to restart guanfacine extended-release tablets with a lower dose Do not take a double dose to make up for a missed dose.
- Guanfacine extended-release tablets should be taken 1 time a day in the morning or in the evening, either alone or in combination with an ADHD stimulant medicine that your doctor may prescribe. Your doctor will tell you when to take guanfacine extended-release tablets and when to take your ADHD stimulant medication.
- Guanfacine extended-release tablets should be swallowed whole with a small amount of water. milk or other liquid.
- Do not crush, chew, or break guanfacine extended-release tablets. Tell your doctor if you cannot swallow guanfacine extended-release tablets whole
- Do not take quanfacine extended-release tablets with a high-fat meal.
- Your doctor will check your blood pressure and heart rate while you take guanfacine extended-release tablets.
- If you take too much quanfacine extended-release tablets, call your local Poison Control Center at 1-800-222-1222 or go to the nearest emergency room right away.

# What should I avoid while taking guanfacine extended-release tablets?

quanfacine extended-release tablets affect you. Guanfacine extended-release tablets can slow

Pharmacist: Detach Here

**Patient Information** 

**Guanfacine Extended-Release Tablets** 

(awahn-fa-seen)

Pharmacist: Detach Here — • Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking

auanfacine extended-release tablets until vou talk with vour doctor. Guanfacine extended-release tablets taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

• Do not become dehydrated or overheated. This may increase your chance of having low blood pressure or fainting while taking guanfacine extended-release tablets.

• Do not suddenly stop quanfacine extended-release tablets. Tell your healthcare provider if you have been vomiting and cannot take guanfacine extended-release tablets, you may be at risk for rebound hypertension.

# What are the possible side effects of guanfacine extended-release tablets?

## Guanfacine extended-release tablets may cause serious side effects including:

- low blood pressure
- low heart rate
- fainting sleepiness
- increased blood pressure and heart rate after suddenly stopping guanfacine extended-release tablets (rebound hypertension). Suddenly stopping quanfacine extended-release tablets can cause increased blood pressure and heart rate and other withdrawal symptoms such as headache, confusion, nervousness, agitation, and tremors. If these symptoms continue to get worse and are left untreated, it could lead to a very serious condition including very high blood pressure, feeling very sleepy or tired, severe headache, vomiting, vision problems, seizures.

## Get medical help right away, if you have any of the symptoms listed above.

# The most common side effects of quantacine extended-release tablets include:

- sleepiness tiredness
- trouble sleeping
- low blood pressure
- nausea
- stomach nair
- dizziness dry mouth
- irritability
- vomiting slow heart rate
- Tell the doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of guanfacine extended-release tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to TWi Pharmaceuticals, Inc. 1-844-518-2989 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

# How should I store guanfacine extended-release tablets?

• Store quanfacine extended-release tablets at 20° to 25°C (68° to 77°F). [see USP Controlled Room Temperature

# Keep guanfacine extended-release tablets and all medicines out of the reach of children. General Information about the safe and effective use guanfacine extended-release

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use guanfacine extended-release tablets for a condition for which it was not prescribed. Do not give guanfacine extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about guanfacine extended-release tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about quanfacine extended-release tablets that is written for health professionals.

# What are the ingredients in quanfacine extended-release tablets? Active ingredient: guanfacine hydrochloride

Inactive ingredients: microcrystalline cellulose, hypromellose, polyvinyl acetate, povidone, lactose monohydrate, magnesium stearate, sodium lauryl sulfate and silica. In addition, the 3 mg and 4 mg tablets also contain FD&C Blue #1.

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Manufactured for:

TWi Pharmaceuticals USA, Inc Paramus, NJ 07652

Manufactured by:

TWI TWi Pharmaceuticals, Inc.

Taoyuan City, 32063, Taiwan Revised: 10/19 OS24979533

Respiratory System: dyspnea

Skin and Appendages: alopecia, dermatitis, exfoliative dermatitis, pruritus, rash

Special Senses: alterations in taste

(12.3)].

Table 14: Clinically Important D	rug Interactions: Effect of other Drugs on	Guantacine Extended-Release Tabl
Concomitant Drug Name or Drug Class	Clinical Rationale and Magnitude of Drug Interaction	Clinical Recommendation
Strong and moderate CYP3A4 inhibitors, e.g., ketoconazole, fluconazole	Guanfacine is primarily metabolized by CYP3A4 and its plasma concentrations can be significantly affected resulting in an increase in exposure	Consider dose reduction [see Dosage and administration (2.7)]
Strong and moderate CYP3A4	Guanfacine is primarily metabolized by	Consider dose increase [see Dosage

be significantly affected resulting in a

# 8 USE IN SPECIFIC POPULATION

### 8.1 Pregnancy Pregnancy Category E

Risk Summary

There are no adequate and well-controlled studies of guanfacine extended-release tablets in pregnant women. No fetal harm wo observed in rats and rabbits with administration of guantacine at 4 and 2.7 times, respectively, the maximum recommended human dose. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Animal data

Reproduction studies conducted in rats have shown that quanfacine crosses the placenta. However, administration of quanfacin to rats and rabbits at 4 and 2.7 times, respectively, the maximum recommended human dose of 0.12 mg/kg/day on a mg/m² basis resulted in no evidence of harm to the fetus. Higher doses (13.5 times the maximum recommended human dose in both rabbits and rats) were associated with reduced fetal survival and maternal toxicity.

are excreted in human milk, caution should be exercised when avanfacine extended release tablets are administered to a nursing woman. Observe human milk-fed infants for sedation and somnolence.

## 8.4 Pediatric Use

Safely and efficacy of guanfacine extended-release tablets in pediatric patients less than 6 years of age have not been established. The efficacy of guanfacine extended-release tablets was studied for the treatment of ADHD in five controlled monotherapy clinical trials (up to 15 weeks in duration), one randomized withdrawal study and one controlled adjunctive trial with psychostimulants (8 weeks in duration) in children and adolescents gaes 6 to 17 who met DSM-IV® criteria for ADHD [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14)7.

In studies in juvenile rats, quanfacine alone produced a slight delay in sexual maturation in males and females at 2 to 3 times In source in overnier man, guardinate interpretate or any interpretate in a combination with methylpheniadae produced of sight delay in sexual maturation and decreased growth as measured by a decrease in bone length in males at a dose of guanfacine comparable to the MRHD and a dose of methylpheniadae approximately 4 times the MRHD.

In a study where juvenile rats were treated with guanfacine alone from 7 to 59 days of age, development was delayed as indicated by a slight delay in sexual maturation and decreased body weight gain in males at 2 mg/kg/day and in females at 3 mg/kg/day. The No Adverse Effect Level (NOAEL) for delayed sexual maturation was 1 mg/kg/day, which is equivalent to the MRHD of 4 mg/day, on a mg/m<sup>2</sup> basis. The effects on fertility were not evaluated in this study.

In a study where juvenile rats were treated with quanfacine in combination with methylphenidate from 7 to 59 days of age, a decrease in ulna hone length and a slight delay in sexual maturation were observed in males given 1 mg/kg/day of aug rease in one one reigin and a signi nearly mescal initiation were asserted in invise given in my gazy or y apun ombination with 2 mg/kg/day of methylpheniators. The NOAELs for these findings were 0.3 mg/kg of guardiscine in bination with 16 mg/kg/day of methylpheniatore, which are equivalent to 0.3 and 1.4 times the MRHD of 4 mg/day and 54 mg/day for guanfacine and methylphenidate, respectively, on a mg/m² basis. These findings were not observed with guanfacine alone at 1 mg/kg/day or methylphenidate alone at 50 mg/kg/day.

The safety and efficacy of quantacine extended-release tablets in geriatric patients have not been established.

8.6 Renal Impairment It may be necessary to reduce the dosage in patients with significant impairment of renal function (see Clinical Pharm (12.3)]

## 8.7 Hepatic Impairme

It may be necessary to reduce the dosage in patients with significant impairment of hepatic function [see Clinical Pharmacology (12.3)].

### 9 DRUG ARUSE AND DEPENDENCE I 9.1 Controlled Substance

ablets are not controlled substance and have no known notential for abuse or dependenc 10 OVERDOSAGE

## Symptoms ... ceting reports of quanfacine overdosage indicate that hypotension, drowsiness, letharay, and bradycardia have bee

Described following overdose, Initial hypertensions may develop early and may be followed by hypotension. Similar symptoms have been described in voluntary reports to the American Association of Poison Control Center's National Poison Data System. Missis of the pupils may be noted on examination. No fatal overdoses of guanfacine have been reported in published literature.

## Consult a Certified Poison Control Center by calling 1-800-222-1222 for up-to-date guidance and advice.

Management of guanfacine extended-release tablets overdose should include monitoring for and the treatment of initial hypertension, if that occurs, as well as hypotension, bradycardia, lethargy and respiratory depression. Children and adolescent who develop letharay should be observed for the development of more serious toxicity including coma, bradycardia and hypotension for up to 24 hours, due to the possibility of delayed onset hypotension

# 11 DESCRIPTION

Guanfacine extended-release tablets are once-daily, extended-release formulation of avanfacine hydrochloride (HCI) in a matrix Obdance Acceled receipts during the Charles and Parket Research (All Parket Research Parket Parket Research Parket P

slightly soluble in acetone. The only organic solvent in which it has relatively high solubility is methanol (>30 mg/mL). Each tablet contains quanfacine HCl equivalent to 1 mg. 2 mg. 3 mg. or 4 mg of quanfacine base. The tablets also contain auter contains gouintecine net equivalent to 1 may, 2 may, 3 may, 61 may a gouinecine microcrystalline cellulose, hypromellose, polyvinyl acetate, povidone, lactose monohyd sulfate and silica. In addition, the 3 mg and 4 mg tablets also contain FD&C Blue #1.

## 12 CLINICAL PHARMACOLOGY

## 1 12.1 Mechanism of Action

Guanfacine is a central alpha $_{2k}$ adrenergic receptor agonist. Guanfacine is not a central nervous system (CNS) stimulant. The mechanism of action of guanfacine in ADHD is not known.

12.2 Pharmacodynamics
Guanfacine is a selective central alpha $_{2k}$ -adrenergic receptor agonist in that it has a 15 to 20 times higher affinity for this receptor subtype than for the alpha $_{2k}$  or alpha $_{2k}$  subtypes.

ınfacine is a known antihypertensive agent. By stimulating central alpha $_{
m 2A}$ -adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in periphera vascular resistance and a reduction in heart rate.

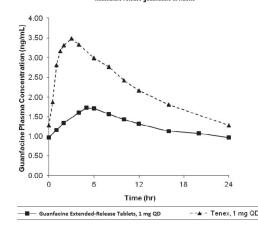
In a thorough QT study, the administration of two dose levels of immediate-release guanfacine (4 mg and 8 mg) produced concentrations approximately 2 to 4 times the concentrations observed with the maximum recommended dose of guanfacine extended-release tablets of 0.12 mg/kg. Guanfacine was not shown to prolong the QTc interval to any clinically relevant exten

Absorption and Distribution Guarfacine is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. After oral

A comparison across studies suggests that the  $C_{max}$  is 60% lower and  $AUC_{0\infty}$  43% lower, respectively, for guanfacine extended-release tablets to immediate-release guanfacine is 58%. The mean pharmacokinetic parameters in adults following th marized in Table 15

### **Guanfacine in Adults** 1 mg once daily 1 mg once daily (n=12) C<sub>mnx</sub> (ng/mL) $1.0 \pm 0.3$ 2.5 ± 0.6 AUC<sub>0.∞</sub> (ng.h/mL) 56 ± 15

are mean +/- SD, except for t<sub>max</sub> which is median (range



exposure to augnfacine was higher in children (gaes 6 to 12) compared to adolescents (gaes 13 to 17) and adults. After oral Exposure to guarantam singles in minimal riggs of the  $T_2$  or indicate statements regions  $T_2$  or  $T_2$  and abuse, zame daministration of multiple doses of guarantam regions  $T_2$  or  $T_2$  and  $T_3$  or  $T_4$  or  $T_4$ The pharmacokinetics were affected by intake of food when a single dose of guanfacine extended-release tablets 4 mg was

# Dose Proportionality

and  $AUC_{0,\infty}$  of quanfacine were proportional to dose.

istered with a high-fat breakfast. The mean exposure increased (C<sub>max</sub> ~75% and AUC ~40%) compared to dosing in a

## Metabolism and Elimination

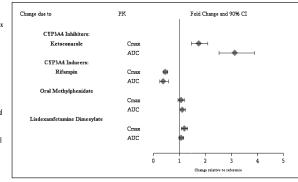
*In vitro* studies with human liver microsomes and recombinant CYP's demonstrated that quanfacine was primarily metabolized by CYP3A4. In pooled human hepotic microsomes, gournfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5); guanfacine is also not an inducer of CYP3A, CYP1A2 and CYP2B6. Guanfacine is a substrate of CYP3A4/5 and exposure is affected by CYP3A4/5 inducers/inhibitors. Guanfacine inhibits MATE1 and OCT1, but does not inhibit BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE2K. administration of guanfacine with OCT1 substrates might potentially increase the exposure of these OCT1 substrates. Studies in Specific Populations

ne impact of renal impairment on the pharmacokinetics of avanfacine in children was not assessed. In adult patients with interruption to return implicit me in primitive transport of the important and function, the cumulative urinary exception of guardacine and the reand clearance diminished as renal function decreased. In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance. The low dialysis clearance was about 15% of the total clearance.

# liver and the kidney, and approximately 50% of the clearance of quanfacine is hepatic [see Hepatic Impairment (8.7)]

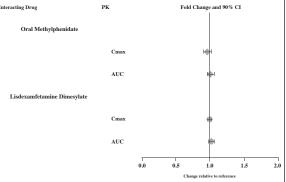
**Drug Interaction Studies** acine is primarily metabolized by CYP3A4 and its plasma concentrations can be affected significantly by CYP3A4 inhibitor

## Figure 2: Effect of Other Drugs on the Pharmacokinetics (PK) of Guanfacine Extended-Release Tablets



Guanfacine does not significantly affect exposures of methylphenidate and lisdexamfetamine when coadministered (Figure 3)

## netics (PK) of Other Drugs



### 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertilit

inogenic effect of auanfacine was observed in studies of 78 weeks in mice or 102 weeks in rats at doses up to 6.8 times

however, a marginal increase in numerical aberrations (polyploidy) was observed in the latter study No adverse effects were observed in fertility studies in male and female rats at doses up to 22 times the maximum reco

human dose on a ma/m2 basis. 14 CLINICAL STUDIES

Efficacy of quanfacine extended

- Five short-term, placebo-controlled monotherapy trials (Studies 1, 2, 4, 5, and 6).
- One short-term, placebo-controlled adjunctive trial with psychostimulants (St
   One long-term, placebo-controlled monotherapy maintenance trial (Study 7)

Studies 1 and 2: Fixed-dose Guanfacine Extended-Release Tablets Monotherapy
Study 1 (301 study) was a double-blind, placebo-controlled, parallel-group, fixed dose study, in which efficacy of once daily
desing with guanfacine extended-release tablets (2 mg, 3 mg and 4 mg) was evaluated for 5 weeks (n-345) in children and adolescents aged 6 to 17 years. Study 2 (304 study) was a double-blind, placebo-controlled, parallel-group, fixed-dose study, in

which efficacy of once daily dosing with guanticane extended-release tablets (1 mg, 2 mg, 3 mg and 4 mg) was evaluated for 6 weeks (n=324) in children and adolescents aged 6 to 17 years. In both studies, randomized patients in 2 mg, 3 mg and 4 mg) was evaluated for 6 weeks (n=324) in children and adolescents aged 6 to 17 years. In both studies, randomized patients in 2 mg, 3 mg and 4 mg dose groups were fitrated to their target fixed dose, and continued on the same dose until a dose tapering phase started. The lowest dose of 1 mg used in Study 2 was not randomized to patients weighing more than 50 kg. Patients who weighed less that

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the Acting the baseline to endpoint in ADHD-RS-VI total scores. Endpoint was defined as the last post-randomization treatment week for which a valid score was obtained prior to dose tapering (up to Week 5 in Study 1 and up to Week 6 in Study 2).

The mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for quantacine extended-release the 2 mg, 3 mg, and 4 mg guanfacine extended-release tablets randomized treatment groups in both studies, as well as the 1 mg guanfacine extended-release tablets treatment group that was included only in Study 2 (see Table 16).

Dose-responsive efficacy was evident, particularly when data were examined on a weight-adjusted (mg/kg) basis. Whe evaluated over the dose range of 0.01 to 0.17 mg/kg/day, clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg/day. Doses up to 0.12 mg/kg/day were shown to provide additional benefit.

In the monotherapy trials (Studies 1 and 2), subgroup analyses were performed to identify any differences in response based o pender or age (6 to 12 vs. 13 to 17). Analyses of the primary outcome did not suggest any differential respon geneter or age (a to 1.2%. 3.10 in 17). Analyses or me primary outcome ato not suggest any curreremian responsiveness on me basis of gender. Analyses by age revealed a statistically significant treatment effect only in the 6 to 12 age subgroup. Due to the relatively small proportion of adolescent patients (ages 13 to 17) enrolled into these studies (approximately 25%), these data may not have been sufficient to demonstrate efficacy in the adolescent patients. In these studies, patients were randomized to a fixed dose of quantacine extended-release tablets rather than optimized by body weight. Therefore, some adolescent patient were randomized to a dose that might have resulted in relatively lower plasma quanticine concentrations compared to younger patients. Over half (55%) of the adolescent patients received doses of 0.01 to 0.04 mg/kg. In studies in which systematic pharmacokinetic data were obtained, there was a strong inverse correlation between body weight and plasm

		Primary Efficacy Measure: ADHD-RS-IV Total Score			
Study Number (Age Range)	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Differencea (95% CI)	
	Guanfacine Extended-Release Tablets 2 mg*	36.1 (9.99)	-15.9 (1.37)	-7.4 (-11.3, -3.5)	
Study 1 (6 to 17 years)	Guanfacine Extended-Release Tablets 3 mg*	36.8 (8.72)	-16.0 (1.38)	-7.5 (-11.4, -3.6)	
(6 to 17 years)	Guanfacine Extended-Release Tablets 4 mg*	38.4 (9.21)	-18.5 (1.39)	-10.0 (-13.9, -6.1)	
Study 2 (6 to 17 years)	Placebo	38.1 (9.34)	-8.5 (1.42)	-	
	Guanfacine Extended-Release Tablets 1 mg*^	41.7 (7.81)	-19.4 (1.69)	-6.8 (-11.3, -2.2)	
	Guanfacine Extended-Release Tablets 2 mg*	39.9 (8.74)	-18.1 (1.60)	-5.4 (-9.9, -0.9)	
	Guanfacine Extended-Release Tablets 3 mg*	39.1 (9.22)	-20.0 (1.64)	-7.3 (-11.8, -2.8)	
	Guanfacine Extended-Release Tablets 4 mg*	40.6 (8.57)	-20.6 (1.60)	-7.9 (-12.3, -3.4)	
	Placebo	39.3 (8.85)	-12.7 (1.60)	-	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; Cl: unad © Difference (drug minus placebo) in least-squares mean change from baseline. ® Doses statistically significantly superior to placebo.

The lowest dose of 1 mg used in Study 2 was not randomized to patients weighing more than 50 kg. Study 3: Flexible-dose Guanfacine Extended-Release Tablets as Adjunctive Therapy to Psychostimulants Study 3 (313 study) was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once dail

optimized dosing (morning or evening) with guarfacine extended-release tablets (1 mg, 2 mg, 3 mg and 4 mg), when upinitized ususing (informing or evening) with grounded restriction of the state of extended-release tablets dose level and were titrated weekly over a 5-week dose-optimization period to an optimal guanfaci extended-release tablets dose not to exceed 4 mg/day based on tolerability and clinical response. The dose was then maintaine for a 3-week dose maintenance period before entry to 1 week of dose tapering. Patients took guanfacine extended-releas To discrete Australiamental period user lein yor in wear on user upening, runeins toos gouinoune exenueur-recess tollables either in the morning or the evening while mointoining their current dose of psychosticululant treatment given each morning. Allowable psychosticulaints in the study were ADDERALL XR®, YYYANSE®, CONCERTA®, FOCALIN XR®, RITALIN LA®, METADATE CD® or FDA-approved generic equivalents.

ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week prior to dose tapering for which a occur, the patient should be advised to discuss the symptoms with the health care provide Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for quanfacine extended-release

Symptoms of ADHD were evaluated on a weekly basis by clinicians using the ADHD Rating Scale (ADHDRS-IV), which includes

tablets given in combination with a psychostimulant compared to placebo given with a psychostimulant for Study 3, for both

morning and evening guanfacine extended-release tablets dosing (see **Table 17**). Nearly two-thirds (64.2%) of patients reached Manufactured for: optimal doses in the 0.05 to 0.12 mg/kg/day range. TWi Pharmaceuticals USA. Inc Paramus NI 07652

### Studies 4, 5 and 6: Flexible-dose Guanfacine Extended-Release Tablets Monotherapy

Study 4 (314 study) was a double-blind, randomized, placebo-controlled, dose-optimization study, in which extended controlled, dose-optimization study, in which extended for 8 weeks dosing (morning or evening) with guardictine extended-release tablets (1 mg, 2 mg, 3 mg, and 4 mg) was evaluated for 8 weeks itudy 4 (314 study) was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once daily Manufactured by:

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating cale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the kate (ADITASTY), which includes soint injecturity important and interiors accusing the juminary entactly outcome was in honge from baseline score at endpoint on the ADITASTY total scores. Andpoint was defined as the last post-randomization reatment week for which a valid score was obtained prior to dose tapering (up to Week 8).

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for quantacine extended-release blets compared to placebo in both AM and PM dosing groups of guanfacine extended-release tablets (see **Table 17**] Study 5 (312 study) was a 15-week, double-blind, randomized, placebo-controlled, dose-optimization study conducted in JOINTY J GITZ SHOPY WAS AT 17-MEER, WORDERMIND, HORDONING PROCESSING AND ADDRESS AND ADDRE Scale-IV (ADHD-RS-IV). Patients receiving guanfacine extended-release tablets showed statistically significantly greater vement on the ADHD-RS-IV total score compared with patients receiving placebo (see Table 17)

Study 6 (316 study) was a 12-week (for children aged 6 to 12) or 15-week (for adolescents aged 13 to 17), randomize aboutserium, parametyrusp, praceus mai rum-erienteinic, uoss-optimizanion suory cinouctei in pienamini parientis (tanienti delofesentis aged fo in 1 years old industrise (n-437) to sesses the efficacy and sefety of once-daily dosing (dildfen: 1 to 4 mg/day, adolescents: 1 to 7 mg/day; optimized dose range of 0.05 to 0.12 mg/kg/day) in the treatment of ADHD. Guanfacine extended-release tablets were statistically superior to placebo on symptoms of ADHD in patients 6 to 17 years a measured by change from baseline in ADHD-RS-IV total scores (see Table 17).

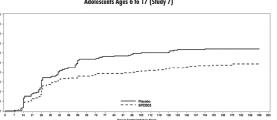
### Table 17: Flevible Doce studies

Study Number (Age Range)	·	Primary Efficacy Measure: ADHD-RS-IV Total Score			
	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>b</sup> (95% CI)	
Study 3a (6 to 17 years)	Guanfacine Extended-Release Tablets 1 to 4 mg AM*	37.6 (8.13)	-20.3 (0.97)	-4.5 (-7.5, -1.4)	
	Guanfacine Extended-Release Tablets 1 to 4 mg PM*	37.0 (7.65)	-21.2 (0.97)	-5.3 (-8.3, -2.3)	
	Placebo	37.7 (7.75)	-15.9 (0.96)	-	
Study 4 (6 to 12 years)	Guanfacine Extended-Release Tablets 1 to 4 mg AM*	41.7 (6.39)	-20.0 (1.23)	-9.4 (-12.8, -6.0)	
	Guanfacine Extended-Release Tablets 1 to 4 mg PM*	41.6 (6.66)	-20.4 (1.19)	-9.8 (-13.1, -6.4)	
	Placebo	42.9 (6.29)	-10.6 (1.20)	-	
Study 5 (13 to 17 years)	Guanfacine Extended-Release Tablets 1 to 7 mg*	39.9 (5.57)	-24.6 (1.06)	-6.03 (-8.87, -3.19)	
	Placebo	40.0 (6.11)	-18.5 (1.08)	-	
Study 6 (6 to 17 years)	Guanfacine Extended-Release Tablets 1 to 7 mg*	43.1 (5.47)	-23.89 (1.15)	-8.88 (-11.94, -5.81)	
	Placebo	43.2 (5.60)	-15.01 (1.16)	-	

SD: standard deviation; SE: standard error; LS Mean; least-squares mean; CI; unadjusted confidence interval a Treatment was given in combination with a psychostimulan

b Difference (drug minus placebo) in least-squares mean change from baseline
 Doses statistically significantly superior to placebo.

Study 7: Long-Term Maintenance of Guanfacine Extended Release Tablets Efficacy
Study 7 (315 study) was a double-blind, placebo-controlled, randomized withdrawal trial in pediatric patients aged 6 to 17 years
with DSM-IV-TR diagnosis of ADHD. The study consisted of an open-label phase, including a 7-week dose optimization period to titrate patients to an optimal dose (maximum 4 ma/day for children and 7 ma/day for adolescents; optimized dose range; 0.05 to 0.12 mg/kg/dgy) and g 6-week dose mainten once period. There were 526 nationts included in the open-label phase. Amon to U.1 z mg/kg/day) and a 6-week dose maintenance period. There were 2/b prients included it in eopen-label phase. Althese, 315 patients who met response criteria in the open-label phase were then randomized. C1, guanfactore extended-rel tablets: placebo] in a 26-week, double-blind, randomized withdrawal phase. The response criteria were defined by ≥ 30% reduction in ADHD-RS-IV total score and a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2 during the open-labe phase. A statistically significantly lower proportion of treatment failures occurred among guanfacine extended-release tablet patients compared to placebo at the end of the randomized withdrawal period (Figure 4). Treatment failure was defined as a potents compared to precess of the end of the state of th



## S HOW SUPPLIED /STORAGE AND HANDLING

uanfacine extended-release tablets are supplied in 1 mg, 2 mg, 3 mg, and 4 mg strength extended-release tablets in 100 count

100 count bottles.						
	1 mg	2 mg	3 mg	4 mg		
r	White	White	Blue	Blue		
ie	Round	Caplet	Round	Caplet		
ossment (top/bottom)	A533/1 mg	A534/ 2 mg	A536/3 mg	A538/ 4 mg		
number	100 count: 24979-533-01	100 count: 24979-534-01	100 count: 24979-536-01	100 count: 24979-538-01		
	1000 count: 24979-533-10	1000 count: 24979-534-10	1000 count: 24979-536-10	1000 count: 24979-538-10		

torage - Store at 20° to 25°C (68° to 77°F). [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). Dosing and Administration

ts to swallow auanfacine extended-release tablets whole with water, milk or other liquid. Tablets should not be usrucz poemis io swaiow gouinacinie extensional ereases routes winde win ware, nimic or onen rigium <u>, toutes stouce</u> mor us usched, chewed or broken prior to diministration because this may increase the rate of relaces of the active <u>nur</u>. Patients hould not take guanfacine extended-release tablets together with a high-fat meal, since this can raise blood levels of guanfacine

extended-release tablets. Instruct the parent or caregiver to supervise the child or adolescent taking guanfacine extender tablets and to keep the bottle of tablets out of reach of children. Advise patients not to abruptly discontinue guanfacine extended-release tablets as abrupt discontinuation can result in clinically significant rebound hypertension. Concomitant stimulant use and abrupt discontinuation of guanfacine extended-release tablet 

Adverse Reactions

Advise patients that sedation can occur, particularly early in treatment or with dose increases. Caution against operating heav equipment or driving until they know how they respond to treatment with guanfacine extended-release tablets [see Warnings and Precautions (5.2)]. Headache and abdominal pain can also occur. If any of these symptoms persist, or other symptoms both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline to endpoint in

> Advise patients to avoid becoming dehydrated or overheated, which may potentially increase the risks of hypotension and syncope [see Warnings and Precautions (5.1)]. Advise patients to avoid use with alcohol.

**Rev. 12**