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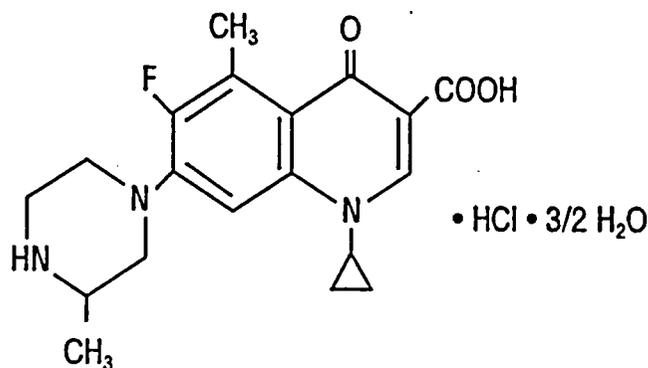
APPROVED LABELING

PRODUCT INFORMATION

RAXAR[®] Tablets**(grepafloxacin hydrochloride tablets)**

DESCRIPTION: RAXAR Tablets contain grepafloxacin hydrochloride. RAXAR is a broad-spectrum fluoroquinolone antimicrobial agent for oral administration.

The chemical name for grepafloxacin is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid monohydrochloride sesquihydrate. Its molecular formula is $C_{19}H_{22}FN_3O_3 \cdot HCl \cdot 3/2 H_2O$ and it has a molecular weight of 422.88. It is soluble in water and very slightly soluble in ethanol. Grepafloxacin has the following structural formula:



RAXAR Tablets are white to pale yellow, film-coated, biconvex, bevel-edged tablets containing either 200 mg, 400 mg, or 600 mg of grepafloxacin base, formulated as a hydrochloride salt. Each tablet contains the following inactive ingredients: low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, magnesium stearate, microcrystalline cellulose, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY:

Absorption: Grepafloxacin is rapidly and extensively absorbed following oral administration of RAXAR Tablets. Bioavailability of the tablet is equivalent to the bioavailability of an oral solution of grepafloxacin. The absolute bioavailability of RAXAR Tablets was estimated by comparing the areas under the plasma grepafloxacin concentration versus time curve (AUC) after intravenous and oral administration of grepafloxacin in separate studies. The absolute bioavailability is approximately 70%.

Single-dose and steady-state pharmacokinetic parameters following administration of 400-mg and 600-mg doses to healthy adult males are displayed in Table 1.

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Table 1: Single-dose and Steady-state Pharmacokinetic Parameters in Healthy Adult Males

Parameter	Single-dose Pharmacokinetic Parameters		Steady-state Pharmacokinetic Parameters	
	400 mg (n = 40)	600 mg (n = 31)	400 mg (n = 10)	600 mg (n = 46)
*AUC (µg•h/mL)	12.27 ± 3.81	22.66 ± 5.65	14.08 ± 2.80	27.51 ± 6.95
C _{max} (µg/mL)	1.11 ± 0.34	1.58 ± 0.37	1.35 ± 0.25	2.25 ± 0.48
Trough (µg/mL)	not applicable	not applicable	0.21 ± 0.08	0.55 ± 0.22

*AUC = AUC_∞ for single dose; AUC₀₋₂₄ for steady state.

On average, the peak plasma drug concentration (C_{max}) is achieved 2 to 3 hours after dosing. Steady-state concentrations of grepafloxacin are achieved within 7 days of once-a-day dosing.

Grepafloxacin pharmacokinetic parameters were determined following administration of 600 mg grepafloxacin immediately following a high fat meal (1000 kcal, 67 grams fat, 38 grams protein, 63 grams carbohydrates) and administration in the fasted state (n = 29). There was no difference in grepafloxacin pharmacokinetic parameters between the fasted and fed treatments. Milk had no effect on the C_{max}, T_{max}, or AUC of grepafloxacin after oral administration. Neutralization of gastric acidity by intravenous administration of the histamine type-2 receptor antagonist famotidine did not affect the absorption or other pharmacokinetic properties of RAXAR Tablets.

Distribution: The apparent volume of distribution after oral administration of grepafloxacin 400 mg was 5.07 ± 0.95 L/kg, suggesting that grepafloxacin distributes widely into extravascular spaces. Binding of grepafloxacin to human plasma proteins is low (approximately 50%).

Table 2 summarizes the concentrations of grepafloxacin in fluids and tissues compared with serum drug concentration.

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Table 2: Distribution of Grepafloxacin into Tissues and Fluids After Oral Administration
(n = number of subjects)

Tissue or Fluid	Oral Dose (mg)	Hours Post-Dose	n	Concentration (Mean ± SD)		
				Serum (µg/mL)	Tissue or Fluid (µg/mL or µg/g)	Ratio
Alveolar lining fluid	400	4-5	5	1.76	27.1	15.4
Alveolar macrophages	400	4-5	5	1.76	278	158
Cervix uteri	100	4-5	5	1.23 ± 0.26	3.42 ± 0.65	2.8
Portio vaginalis	100	4-5	5	1.23 ± 0.26	2.58 ± 0.69	2.1
Sputum	200	4	7	0.47 ± 0.11	1.04 ± 0.48	2.2

Metabolism and Excretion: The plasma elimination half-life of grepafloxacin at steady state was 15.7 ± 4.2 hours. Grepafloxacin is eliminated predominantly through hepatic metabolism and biliary excretion. Less than 10% of an oral dose is excreted as unchanged grepafloxacin in urine. Approximately 88% of an oral dose of radiolabeled grepafloxacin 400 mg was recovered in urine (38%) and feces (50%) over 7 days post dose. Approximately one half of the AUC in plasma for the 12 hours after dosing was due to unchanged grepafloxacin; 68% of AUC in plasma for 12 hours after dosing was due to unchanged grepafloxacin plus known metabolites. Unchanged grepafloxacin (6% of dose) and several metabolites (in amounts ranging from 0.08% to 5.57% of dose) were recovered in urine. Unchanged grepafloxacin (27% of dose) and several metabolites (in amounts ranging from 1.83% to 3.91% of dose) were recovered in feces. Grepafloxacin metabolites include glucuronide (major metabolite) and sulfate conjugates and oxidative metabolites. The oxidative metabolites are formed mainly by cytochrome P450 1A2 (CYP1A2), while the cytochrome P450 3A4 (CYP3A4) has minor involvement. The nonconjugated metabolites have little antimicrobial activity compared with the parent drug. The conjugated metabolites have no antimicrobial activity.

Special Populations: Gender: Following administration of RAXAR 600 mg daily for 7 days, C_{max} was approximately 30% to 50% higher and AUC was approximately 20% to 50% higher in females compared to males. The observed differences appear to be due mainly to differences in body weight. Total clearance (per unit body weight), renal clearance (per unit body weight), and half-life did not differ between males and females. The observed differences in pharmacokinetic properties by gender do not necessitate any difference between males and females in dosage and administration.

Geriatric: There are no significant differences in grepafloxacin pharmacokinetics between young and elderly subjects.

Pediatric: Grepafloxacin has not been evaluated in pediatric patients.

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76 **Hepatic Insufficiency:** Two studies were performed to assess the effect of hepatic failure on
77 grepafloxacin pharmacokinetics. Both studies evaluated subjects with normal hepatic function, with mild
78 (Child-Pugh class A) hepatic failure, or moderate hepatic failure (Child-Pugh class B). In one study, oral
79 clearance was reduced by approximately 50% in patients with mild hepatic failure (n = 5) relative to
80 subjects with normal hepatic function (n = 6). In the second study, oral clearance was reduced by
81 approximately 15% in subjects with mild hepatic failure (n = 5) relative to subjects with normal hepatic
82 function (n = 8). Due to the different results for the two studies, it is not possible to determine an
83 appropriate dose adjustment for subjects with mild hepatic failure. In both studies, oral clearance was
84 decreased by >50% in subjects with moderate hepatic failure (n = 9, n = 3) compared to subjects with
85 normal hepatic function (n = 6, n = 8). RAXAR Tablets are contraindicated for use in patients with hepatic
86 failure (see **DOSAGE AND ADMINISTRATION**).

87 **Renal Insufficiency:** Renal clearance of grepafloxacin was 0.458 ± 0.04 mL/min per kg in adults with
88 normal renal function. The effect of varying degrees of renal function on the pharmacokinetics of
89 grepafloxacin was assessed in 15 patients with impaired renal function (creatinine clearances ranging
90 from 7.5 to 64 mL/min) compared with five adults with normal renal function. Varying degrees of renal
91 function did not substantially affect the pharmacokinetic properties of grepafloxacin.

92 **Smokers:** In a population pharmacokinetics study of grepafloxacin in patients with acute bacterial
93 exacerbations of chronic bronchitis, grepafloxacin clearance was 35% to 43% faster in patients who
94 smoked relative to patients who did not smoke. This observation is consistent with the involvement of
95 CYP1A2 in the metabolism of grepafloxacin and the known induction of this enzyme in smokers.
96 However, in the pivotal clinical trials, smoking did not have an effect on clinical efficacy.

97 **Drug Interactions:** (See also **PRECAUTIONS**.)

98 **Antacids:** Following administration of 200 mg grepafloxacin with 1 gram aluminum hydroxide,
99 grepafloxacin AUC and C_{max} were both decreased by approximately 60% relative to administration of
100 grepafloxacin alone (n = 6) (see **PRECAUTIONS**).

101 **Probenecid:** Administration of 200 mg grepafloxacin with 500 mg probenecid, followed by 500 mg
102 probenecid every 12 hours for three doses, did not alter grepafloxacin pharmacokinetics (n = 6).

103 **Theophylline:** Grepafloxacin is a competitive inhibitor of theophylline metabolism. Twelve healthy
104 subjects received an individualized regimen of sustained-release theophylline alone for 7 days, followed
105 by coadministration of the theophylline regimen with 600 mg grepafloxacin once daily for 10 days.
106 Following the addition of grepafloxacin, theophylline clearance decreased by approximately 50%, from
107 0.78 ± 0.25 to 0.40 ± 0.08 mL/min per kg. Steady-state peak theophylline concentration increased from
108 8.30 ± 1.54 μ g/mL to 15.12 ± 3.69 μ g/mL (see **PRECAUTIONS**):

109 **Warfarin:** Fourteen healthy subjects received an individualized regimen of warfarin alone for 14 days,
110 followed by coadministration of the warfarin regimen with 600 mg grepafloxacin once daily for 10 days.
111 Grepafloxacin did not alter the anticoagulant effect of warfarin. Other quinolones have been reported to
2 enhance the anticoagulant effects of warfarin (see **PRECAUTIONS**).

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Microbiology: Grepafloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative aerobic microorganisms, as well as some atypical microorganisms. Grepafloxacin exerts its antibacterial activity by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, essential enzymes for duplication, transcription, and repair of bacterial DNA. Beta-lactamase production has no effect on grepafloxacin activity and penicillin-resistant *Streptococcus pneumoniae* strains have undiminished *in vitro* susceptibility to grepafloxacin. Grepafloxacin is bactericidal at concentrations equal to or slightly greater than minimum inhibitory concentrations (MICs).

Resistance to grepafloxacin through spontaneous mutation *in vitro* occurs at a low frequency (10^{-8} to 10^{-10}). As with other fluoroquinolones, the mutation frequency was higher for *Pseudomonas* species and *Stenotrophomonas maltophilia* than for other microorganisms. When resistance develops, it does so through slow stepwise increases in MICs. In clinical trials, grepafloxacin-resistant mutants were rarely encountered during the treatment of infections caused by susceptible isolates. When they did occur, they were usually *Pseudomonas* species isolates.

Although cross-resistance has been observed between grepafloxacin and some other fluoroquinolones, some organisms resistant to other quinolones are susceptible to grepafloxacin.

Quinolones differ in chemical structure and mode of action from other classes of antimicrobial agents, including beta-lactam antibiotics and aminoglycosides; therefore, microorganisms resistant to these other classes of drugs may be susceptible to grepafloxacin and other quinolones.

In vitro tests show that grepafloxacin has reduced activity against some gram-positive microorganisms when combined with rifampin.

Grepafloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic Gram-positive Microorganisms:

Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic Gram-negative Microorganisms:

Haemophilus influenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

Other Microorganisms:

Chlamydia trachomatis

Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown.

Grepafloxacin exhibits *in vitro* MICs of 1 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of grepafloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive Microorganisms:

Staphylococcus aureus (methicillin-susceptible strains)

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151 *Staphylococcus epidermidis* (methicillin-susceptible strains)

152 *Streptococcus agalactiae*

153 *Streptococcus pneumoniae* (penicillin-resistant strains)

154 *Streptococcus pyogenes*

155 **Aerobic Gram-negative Microorganisms:**

156 *Citrobacter freundii*

157 *Citrobacter (diversus) koseri*

158 *Enterobacter aerogenes*

159 *Enterobacter cloacae*

160 *Escherichia coli*

161 *Haemophilus parainfluenzae*

162 *Klebsiella oxytoca*

163 *Klebsiella pneumoniae*

164 *Morganella morganii*

165 *Proteus mirabilis*

166 *Proteus vulgaris*

167 **Other Microorganisms:**

168 *Legionella pneumophila*

169

170 **Susceptibility Tests: Dilution Techniques:** Quantitative methods are used to determine MICs. These
171 MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be
172 determined using a standardized procedure. Standardized procedures are based on a dilution method¹
173 (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations
174 of grepafloxacin powder. The MIC values should be interpreted according to the following criteria:

175 For testing aerobic organisms other than *Streptococcus pneumoniae*, *Haemophilus influenzae*, and
176 *Neisseria gonorrhoeae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

177

178 For testing *Streptococcus pneumoniae*:[▪]

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤1	Susceptible (S)

179 [▪] These interpretive standards are applicable only to broth microdilution susceptibility tests using
180 cation-adjusted Mueller-Hinton broth with 2% to 5% lysed horse blood.

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The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Haemophilus influenzae*:^b

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤0.25	Susceptible (S)

^bThese interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).¹

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*:^c

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤0.06	Susceptible (S)

^cThese interpretive standards are applicable only to agar dilution tests with GC agar base and 1% defined growth supplement.

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard grepafloxacin powder should provide the following MIC values:

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<u>Microorganism</u>	<u>MIC Range (µg/mL)</u>
<i>Escherichia coli</i> ATCC 25922	0.004-0.03
<i>Haemophilus influenzae</i> ATCC 49247 ^a	0.002-0.016
<i>Neisseria gonorrhoeae</i> ATCC 49226 ^b	0.004-0.03
<i>Staphylococcus aureus</i> ATCC 29213	0.03-0.12
<i>Streptococcus pneumoniae</i> ATCC 49619 ^c	0.06-0.5

211 ^a This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a broth
212 microdilution procedure using HTM.¹

213 ^b This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by agar dilution
214 using GC agar base with 1% defined growth supplement.

215 ^c This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a broth
216 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2% to 5% lysed horse blood.

217

218 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also
219 provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such
220 standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses
221 paper disks impregnated with 5-µg grepafloxacin to test the susceptibility of microorganisms to
222 grepafloxacin.

223 Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg
224 disk should be interpreted according to the following criteria:

225 For aerobic organisms other than *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria*
226 *gonorrhoeae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥18	Susceptible (S)
15 - 17	Intermediate (I)
≤14	Resistant (R)

227

228 For testing *Streptococcus pneumoniae*:^a

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥19	Susceptible (S)

229 ^a These zone diameter standards for *Streptococcus pneumoniae* are applicable only to tests performed
230 using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO₂.

231

232 The current absence of data on resistant strains precludes defining any categories other than
233 "Susceptible." Strains yielding zone diameter results suggestive of a "Nonsusceptible" category should be
234 submitted to a reference laboratory for further testing.

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235 For testing *Haemophilus influenzae*:^b

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥24	Susceptible (S)

236 ^b These zone diameter standards are applicable only to disk diffusion testing with *Haemophilus*
237 *influenzae* using HTM.²

238

239 The current absence of data on resistant strains precludes defining any categories other than
240 "Susceptible." Strains yielding zone diameter results suggestive of a "Nonsusceptible" category should be
241 submitted to a reference laboratory for further testing.

242 For testing *Neisseria gonorrhoeae*:^c

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥37	Susceptible (S)

243 ^c These zone diameter standards for *Neisseria gonorrhoeae* are applicable only to disk diffusion tests
244 with GC agar base and 1% growth supplement.

245

246 The current absence of data on resistant strains precludes defining any categories other than
247 "Susceptible." Strains yielding zone diameter results suggestive of a "Nonsusceptible" category should be
248 submitted to a reference laboratory for further testing.

249 Interpretation should be as stated above for results using dilution techniques. Interpretation involves
correlation of the diameter obtained in the disk test with the MIC for grepafloxacin.

251 As with standardized dilution techniques, diffusion methods require the use of laboratory control
252 microorganisms that are used to control the technical aspects of the laboratory procedures. For the
253 diffusion technique, the 5-µg grepafloxacin disk should provide the following zone diameters in these
254 laboratory test quality control strains:

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i> ATCC 25922	28-36
<i>Haemophilus influenzae</i> ATCC 49247 ^a	32-39
<i>Neisseria gonorrhoeae</i> ATCC 49226 ^b	44-52
<i>Staphylococcus aureus</i> ATCC 25923	26-31
<i>Streptococcus pneumoniae</i> ATCC 49619 ^c	21-28

255 ^a This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion
256 procedure using HTM.²

257 ^b This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by a disk diffusion
258 procedure using GC agar base with 1% defined growth supplement.

259 ^c This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a disk diffusion
260 procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO₂.

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INDICATIONS AND USAGE: RAXAR Tablets are indicated for treatment of adults with mild to moderate infections caused by susceptible strains of the designated microorganisms in the infections listed below:

1. **Acute Bacterial Exacerbations of Chronic Bronchitis** caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis* (see **CLINICAL STUDIES** section).
2. **Community-acquired Pneumonia** caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Mycoplasma pneumoniae* (see **CLINICAL STUDIES** section).
3. **Uncomplicated Gonorrhea** (urethral in males and endocervical and rectal in females) caused by *Neisseria gonorrhoeae* (see **WARNINGS**).
4. **Nongonococcal Urethritis and Cervicitis** caused by *Chlamydia trachomatis* (see **WARNINGS**).

Appropriate culture and susceptibility testing should be performed to determine susceptibility of the causative microorganism(s) to grepafloxacin. Therapy may be started while awaiting the results of this testing. Antimicrobial therapy should be appropriately adjusted according to the results of such testing.

CONTRAINDICATIONS: RAXAR Tablets are contraindicated in persons with a history of hypersensitivity to grepafloxacin or other members of the quinolone class of antimicrobial agents. RAXAR Tablets are contraindicated in patients with hepatic failure. Because prolongation of the QT_c interval has been observed in healthy volunteers receiving RAXAR, RAXAR Tablets are contraindicated in patients with known QT_c prolongation. RAXAR Tablets are also contraindicated in patients being treated concomitantly with medications known to produce an increase in the QT_c interval and/or torsade de pointes (e.g., terfenadine) unless appropriate cardiac monitoring can be assured (e.g., in hospitalized patients) (see **WARNINGS**).

WARNINGS: THE SAFETY AND EFFICACY OF GREPAFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED (SEE PRECAUTIONS - PEDIATRIC USE, PREGNANCY, AND NURSING MOTHERS SUBSECTIONS). Histopathological examination of the weight-bearing joints of juvenile dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (see **ANIMAL PHARMACOLOGY**).

Convulsions have been reported in patients receiving quinolones, including grepafloxacin. Increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system stimulation that may lead to tremors, restlessness, lightheadedness, confusion, or hallucinations. If these reactions occur in patients receiving grepafloxacin, the drug should be discontinued and appropriate treatment measures instituted. As with other quinolones, RAXAR should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures (see **ADVERSE REACTIONS**).

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300 In healthy male and female volunteers who received RAXAR, prolongation of the QT_c interval was
301 observed. Because of a potential risk of cardiac arrhythmias, including torsade de pointes, patients
302 receiving RAXAR should avoid concomitant treatment with medications known to prolong the QT_c interval,
303 e.g., class I antiarrhythmic agents (e.g., quinidine, procainamide), class III antiarrhythmic agents (e.g.,
304 amiodarone, sotalol), and bepridil, as well as erythromycin, terfenadine, astemizole, cisapride,
305 pentamidine, tricyclic antidepressants, and some antipsychotics, including phenothiazines, when
306 appropriate cardiac monitoring cannot be assured, e.g., during outpatient therapy (see
307 **CONTRAINDICATIONS**). RAXAR is not recommended for use in patients with ongoing pro-arrhythmic
308 conditions (e.g., hypokalemia, significant bradycardia, congestive heart failure, myocardial ischemia, and
309 atrial fibrillation).

310 Serious and occasionally fatal hypersensitivity (anaphylactoid or anaphylactic) reactions have been
311 reported in patients receiving therapy with quinolones, often following the first dose. Some reactions have
312 been accompanied by cardiovascular collapse, hypotension, shock, seizure, loss of consciousness,
313 tingling, angioedema, (including tongue, laryngeal, throat, or facial edema/swelling, etc.), airway
314 obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea,
315 urticaria/hives, itching, and other serious skin reactions. Only a few of these patients had a history of prior
316 hypersensitivity reactions. Allergic reactions of varying severity, including anaphylactic shock and
317 anaphylactoid reactions, have occurred in patients receiving grepafloxacin. Grepafloxacin should be
318 discontinued if an allergic reaction or any other sign of hypersensitivity appears. Serious acute
319 hypersensitivity reactions require immediate treatment.

320 Serious and sometimes fatal events of uncertain etiology have been reported in patients receiving
321 therapy with quinolones. Serious events are extremely rare and generally occur following administration
322 of multiple doses. Clinical manifestations of serious adverse events may include one or more of the
323 following: fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson
324 syndrome, etc.); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis; interstitial nephritis,
325 acute renal insufficiency/failure; hepatitis, jaundice, acute hepatic necrosis/failure; tendon pain,
326 inflammation, or rupture; anemia (including hemolytic and aplastic anemia), thrombocytopenia, including
327 thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other
328 hematologic abnormalities. Grepafloxacin should be discontinued immediately at the first appearance of
329 any such reaction and appropriate intervention should be instituted (see **PRECAUTIONS: Information**
330 **for Patients and ADVERSE REACTIONS**).

331 The efficacy of grepafloxacin for treatment of syphilis is not known. Antimicrobial agents used in high
332 doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis.
333 All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients
334 treated with grepafloxacin should have a follow-up serologic test for syphilis 3 months after treatment for
335 gonorrhea.

336 Pseudomembranous colitis has been reported with nearly all antibacterial agents, including
337 quinolones, and may range in severity from mild to life-threatening. Therefore, it is important to

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338 consider this diagnosis in patients who present with diarrhea subsequent to the administration of
339 antibacterial agents.

340 Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of
341 clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of
342 "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established,
343 therapeutic measures should be initiated.

344 Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have
345 been reported in patients receiving quinolone antibiotics. Grepafloxacin should be discontinued if the
346 patient experiences pain, inflammation, or rupture of a tendon (see **PRECAUTIONS: Information for**
347 **Patients**).

348

349 **PRECAUTIONS:**

350 **General:** Phototoxicity reactions have been observed in patients who were exposed to direct sunlight or
351 tanning booths while receiving some quinolones, including grepafloxacin. Excessive sunlight should be
352 avoided. Therapy should be discontinued if phototoxicity occurs.

353 **Information for Patients:** Patients should be advised:

- 354
- 355 • that grepafloxacin may be taken with or without meals.
 - 356 • that grepafloxacin increases the effects of theophylline, and to advise their physician immediately if
357 they are taking theophylline.
 - 358 • that multivitamins (containing iron or zinc), antacids (containing magnesium, calcium, or aluminum),
359 sucralfate, or VIDEX® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution
360 should not be taken within 4 hours before or 4 hours after taking grepafloxacin (see **PRECAUTIONS:**
361 **Drug Interactions**).
 - 362 • that grepafloxacin may increase the effects of other drugs metabolized by the liver, and to advise their
363 physician of any of the drugs they are taking.
 - 364 • to drink fluids liberally.
 - 365 • that grepafloxacin may increase the effects of caffeine.
 - 366 • that grepafloxacin may be associated with hypersensitivity reactions, even following a single dose,
367 and to discontinue the drug at the first sign of skin rash, hives, or other skin reactions, a rapid
368 heartbeat, difficulty in swallowing or breathing, or any other symptom of an allergic reaction (see
369 **WARNINGS**).
 - 370 • that grepafloxacin may cause dizziness and lightheadedness; therefore, patients should know how
371 they react to this drug before they operate an automobile or machinery or engage in activities
372 requiring mental alertness and coordination.
 - 373 • to discontinue treatment; rest and refrain from exercise; and to contact their physician immediately if
they experience pain, inflammation, or rupture of a tendon.

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- to avoid excessive sunlight or artificial ultraviolet light while taking grepafloxacin and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin eruptions) occurs.
- that convulsions have been reported in patients taking quinolones, including grepafloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: (See also CLINICAL PHARMACOLOGY: Drug Interactions.)

Antacids, Sucralfate, Metal Cations, Multivitamins: Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing aluminum, magnesium, or calcium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as VIDEX (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. These agents should not be taken within 4 hours before or 4 hours after grepafloxacin administration.

Caffeine, Theobromine: Grepafloxacin, like other quinolones, may inhibit the metabolism of caffeine and theobromine. These stimulants are commonly found in coffee and tea, respectively. In some patients, this may lead to reduced clearance, prolongation of plasma half-life, and enhanced effects of caffeine and theobromine.

Theophylline: Grepafloxacin is a competitive inhibitor of the metabolism of theophylline. Serum theophylline concentrations increase when grepafloxacin is initiated in a patient maintained on theophylline. When initiating a multi-day course of grepafloxacin in a patient maintained on theophylline, the theophylline maintenance dose should be halved for the period of concurrent use of grepafloxacin and monitoring of serum theophylline concentrations should be initiated as a guide to further dosage adjustments.

Warfarin: In subjects receiving warfarin, no significant change in clotting time was observed when grepafloxacin was coadministered. However, because some quinolones have been reported to enhance the effects of warfarin or its derivatives, prothrombin time or other suitable anticoagulation test should be monitored closely if a quinolone antimicrobial is administered with warfarin or its derivatives.

Drugs Metabolized by Cytochrome P450 Enzymes: The drug interaction study evaluating the effect of grepafloxacin on theophylline indicates that grepafloxacin inhibits theophylline metabolism, which is mediated by CYP1A2. While no clinical studies have been conducted to evaluate the effect of grepafloxacin on the metabolism of CYP3A4 substrates, *in vitro* data suggest similar effects of grepafloxacin in CYP3A4-mediated metabolism and theophylline metabolism. In addition, other quinolones have been reported to decrease the CYP3A4-mediated metabolism of cyclosporine. Other drugs metabolized by CYP3A4 include terfenadine, astemizole, cisapride, midazolam, and triazolam. The clinical relevance of the potential effect of grepafloxacin on the metabolism of CYP3A4 substrates is not known. Patients receiving concurrent administration of substrates of CYP3A4 were not excluded from clinical trials of grepafloxacin.

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10 **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):** The concomitant administration of a nonsteroidal
11 anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions (see
412 **WARNINGS**).

413 **Antidiabetic Agents:** Disturbances of blood glucose, including hyperglycemia and hypoglycemia,
414 have been reported in patients treated concomitantly with quinolones and an antidiabetic agent.

415 Therefore, careful monitoring of blood glucose is recommended when these agents are coadministered.

416 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies to determine the
417 carcinogenic potential of grepafloxacin hydrochloride have not been performed. Grepafloxacin was not
418 mutagenic in the Ames test, a forward gene mutation assay, mouse micronucleus assay, and an assay of
419 unscheduled DNA repair (UDS) using rat hepatocytes. Grepafloxacin was mutagenic in a bacterial DNA
420 repair test and in an *in vitro* chromosome aberration test.

421 In a rat intravenous fertility study, grepafloxacin produced no drug-related changes in the estrous cycle
422 of females; copulation or fertility of males or females.

423 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Grepafloxacin had neither embryoletal nor
424 teratogenic effects in rats when administered orally or intravenously. There was no compound-related
425 effect on maintenance of pregnancy, parturition, implantation of females, ovulation, nursing, or on
426 viability, body weight, or morphology of fetuses. However, a decrease in placental weight and in the
427 number of ossified sacrococcygeal vertebrae were observed in rats at 2.4 times the recommended
428 maximum daily human dose based on mg/m² (15 times the recommended maximum daily human dose
429 on a mg/kg basis); this was associated with maternal toxicity (decreased body weight and food
430 consumption). No effect was noted at 420 mg/m² per day (equivalent to the human dose).

431 Grepafloxacin had no embryoletal or teratogenic effects in rabbits. However, fetal body weight was
432 suppressed and there was a tendency for a decrease in placental weight at 60-mg/kg doses. Maternal
433 toxicity was demonstrated by abortion in rabbits at doses of 40 mg/kg or higher, a finding which is
434 common in reproductive studies with antibacterial agents in rabbits.

435 In a perinatal/postnatal study in rats, death and prolongation of delivery time were observed at
436 2.4 times the recommended maximum daily human dose based on a mg/m² basis (15 times the
437 recommended maximum daily human dose on a mg/kg basis). There was no drug-related effect on
438 delivery index, lactation, or offspring.

439 Adequate and well-controlled studies have not been conducted in pregnant women. Grepafloxacin
440 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see
441 **WARNINGS**).

442 **Nursing Mothers:** Grepafloxacin is excreted in human milk. Grepafloxacin was detectable in breast milk
443 of one patient who was studied on the ninth day of treatment at 4 to 5 hours after oral administration of
444 400 mg of grepafloxacin.

445 Blood and milk concentrations of radioactivity were determined after oral administration of radiolabeled
446 grepafloxacin at a dose of 40 mg/kg in lactating rats at 12 to 13 days post partum. The concentration of
447 radioactivity in milk reached a maximum of 9.03 µg Eq/mL at 1 hour after administration and decreased to

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18 3.20 µg Eq/mL at 24 hours after administration. The AUC_(0-48 h) of radioactivity concentration in milk was
49 16 times that observed in the blood.

450 It is known that other quinolones are excreted in human milk. Because of the potential for serious
451 adverse experiences from grepafloxacin in nursing infants, a decision should be made to discontinue
452 nursing or discontinue administration of the drug, taking into account the importance of this drug to the
453 mother (see **WARNINGS**).

454 **Geriatric Use:** Of the total number of subjects in clinical studies of RAXAR, 409 were 65 and over, while
455 104 were 75 and over. No overall differences in safety or effectiveness were observed between these
456 subjects and younger subjects, and other reported clinical experience has not identified differences in
457 responses between the elderly and younger patients, but greater sensitivity of some older individuals
458 cannot be ruled out.

459 **Pediatric Use:** The safety and effectiveness of grepafloxacin in pediatric patients and adolescents less
460 than 18 years of age have not been established.

461
462 **ADVERSE REACTIONS:** Adverse reactions were assessed in clinical trials involving approximately
463 2500 patients receiving single-dose or multiple-dose regimens of grepafloxacin.

464 **Multiple-dose Regimens:** Most of the adverse reactions reported in clinical trials were transient in
465 nature, mild to moderate in severity, and required no treatment. Twenty of 1069 patients (1.9%) receiving
466 grepafloxacin 400 mg daily and 50 of 925 patients (5.4%) receiving grepafloxacin 600 mg daily
467 discontinued RAXAR Tablets due to an adverse reaction thought by the investigator to be drug-related.

468 Table 3 lists adverse events that occurred with frequencies of 1% or greater. These events were
469 thought by the investigators to be drug-related in patients treated with grepafloxacin in multiple-dose
470 clinical trials.

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**Table 3: Drug-Related Adverse Reactions in Grepafloxacin-Treated Patients
on Multiple-dose Dosing Regimens in Clinical Trials**

Adverse Reaction	400 mg daily (n = 1069)	600 mg daily (n = 925)
Nausea	11.1%	15.8%
Taste perversion	9.0%	17.8%
Headache	4.6%	4.9%
Dizziness	4.3%	5.4%
Diarrhea	3.5%	4.2%
Vaginitis	3.3%	1.4%
Abdominal pain	2.2%	2.1%
Vomiting	1.7%	5.7%
Pruritus	1.6%	1.2%
Dyspepsia	1.5%	3.1%
Leukorrhea	1.4%	0.0%
Asthenia	1.4%	2.3%
Infection	1.3%	0.4%
Insomnia	1.3%	2.1%
Rash	1.1%	1.9%
Anorexia	0.8%	1.8%
Somnolence	1.0%	1.5%
Dry mouth	0.8%	1.1%
Photosensitivity reaction	0.7%	1.8%
Constipation	0.7%	2.2%
Pain	0.6%	1.0%
Nervousness	0.6%	1.7%

474

Additional drug-related events, occurring in multiple-dose clinical trials at a rate of less than 1%, were:

475

476

Body as a Whole: Back pain, body odor, chest pain, chills, facial edema, fever, malaise, neck rigidity, pelvic pain.

477

478

Cardiovascular System: Arrhythmia, hypotension, palpitations, peripheral vascular disorder, postural hypotension, syncope, tachycardia, vasodilatation.

479

480

Digestive System: Abnormal liver function tests, abnormal stools, cheilitis, dysphagia, eructation, flatulence, gastritis, gastrointestinal disorder, gingivitis, glossitis, increased appetite, melena, mouth ulceration, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue discoloration, tongue disorder, tongue edema.

481

482

483

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74 **Hemic and Lymphatic System:** Anemia, eosinophilia, hypochromic anemia, leukocytosis,
35 leukopenia, lymphadenopathy, lymphocytosis, lymphoma-like reaction, prothrombin decreased,
486 prothrombin increased, reticuloendothelial hyperplasia, thrombocytopenia, thromboplastin increased.

487 **Metabolic and Nutritional System:** Dehydration, edema, electrolyte abnormality, gout,
488 hyperglycemia, hyperlipidemia, hypernatremia, hyperuricemia, increased alkaline phosphatase, increased
489 BUN, increased creatinine, increased gamma glutamyl transpeptidase, increased SGOT, increased
490 SGPT, peripheral edema, weight loss.

491 **Musculoskeletal System:** Arthralgia, myalgia.

492 **Nervous System:** Abnormal dreams, abnormal gait, agitation, anxiety, confusion, depression,
493 emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, paresthesia, speech disorder,
494 stupor, thinking abnormal, tremor, vertigo.

495 **Respiratory System:** Asthma, atelectasis, bronchitis, dyspnea, epistaxis, hemoptysis, increased
496 cough, laryngismus, pharyngitis, pleural effusion, rhinitis, sputum increased.

497 **Skin and Appendages:** Acne, alopecia, dry skin, epidermal necrolysis, exfoliative dermatitis, fungal
498 dermatitis, herpes simplex, maculopapular rash, skin disorder, sweating, urticaria, vesiculobullous rash.

499 **Special Senses:** Amblyopia, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, lacrimation
500 disorder, parosmia, photophobia, taste loss, tinnitus.

501 **Urogenital System:** Albuminuria, balanitis, dysuria, hematuria, impotence, polyuria, urethral pain,
502 uricaciduria, urinary frequency, urinary tract disorder, urination impaired, urine abnormality, vulvovaginal
503 disorder.

504 **Single-dose Regimens:** In clinical trials, patients were treated for uncomplicated gonorrhea using a
505 single dose of RAXAR 400 mg. There were no deaths or permanent disabilities in these studies.

506 Table 4 lists the adverse events which occurred with frequencies of 1% or greater. These events were
507 thought by the investigators to be drug-related in patients treated with RAXAR Tablets in single-dose
508 clinical trials.

509

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**Table 4: Drug-Related Adverse Reactions in Grepafloxacin-Treated Patients
on a Single-dose Dosing Regimen in Clinical Trials**

Adverse Reaction	400 mg daily (n = 487)
Vaginitis	5.0%
Nausea	3.3%
Dizziness	2.1%
Vomiting	2.1%
Headache	1.8%
Leukorrhea	1.2%
Abdominal pain	1.2%
Diarrhea	1.2%
Pruritus	1.2%
Taste perversion	1.2%

Additional drug-related events, occurring in single-dose clinical trials at a rate of less than 1%, were:

Body as a Whole: Asthenia, chest pain, chills, flu-like syndrome, infection, malaise.

Cardiovascular System: Syncope, vasodilatation.

Digestive System: Anorexia, constipation, increased appetite, tenesmus.

Hemic and Lymphatic System: Lymphadenopathy.

Nervous System: Hyperkinesia, insomnia, nervousness, somnolence.

Respiratory System: Rhinitis.

Skin and Appendages: Acne, rash, sweating.

Urogenital System: Balanitis.

Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of grepafloxacin formulations. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to grepafloxacin.

Eye: Disturbances in vision.

Non-Site-specific: Allergic reactions, including anaphylactoid reaction/anaphylactic shock, angioedema, laryngeal edema.

OVERDOSAGE: In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. As with other quinolones, adequate hydration and electrolyte balance must be maintained. Due to the possibility of prolongation of the QT_c interval and complications including arrhythmias, ECG monitoring is

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536 recommended after overdosage with RAXAR. It is not known if grepafloxacin can be efficiently removed
537 by hemodialysis or peritoneal dialysis.

538 At oral doses of 4500 mg/kg (14,400 mg/m²) in mice and 3000 mg/kg (21,000 mg/m²) in rats,
539 significant increases in mortality were noted. These doses were approximately equivalent to 39 (mice)
540 and 57 (rats) times the human dose on a mg/m² basis.

541
542 **DOSAGE AND ADMINISTRATION:** RAXAR Tablets may be taken with or without meals. Sucralfate;
543 antacids containing magnesium, calcium, or aluminum; multivitamins containing iron or zinc; or VIDEX
544 (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within
545 4 hours before or 4 hours after taking grepafloxacin. The usual dose for RAXAR is 400 mg or 600 mg
546 orally every 24 hours as described in Table 5.

547
548 **Table 5: Recommended Daily Dosages**
549

Infection*	Dose	Frequency	Duration (days)
Acute bacterial exacerbations of chronic bronchitis [†]	400 or 600 mg	once daily	10
Community-acquired pneumonia	600 mg	once daily	10
Nongonococcal urethritis or cervicitis	400 mg	once daily	7
Uncomplicated gonorrhea	400 mg	single dose	1

550 * DUE TO THE DESIGNATED PATHOGENS (see INDICATIONS AND USAGE).

551 [†] See CLINICAL STUDIES section.

552
553 As with other broad-spectrum antimicrobial agents, prolonged use of grepafloxacin may result in
554 overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial
555 susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be
556 taken.

557 **Patients with Renal Failure:** Dosage adjustment is not required in patients with impaired renal function.

558 **Patients with Hepatic Disease:** Metabolism and excretion of grepafloxacin are reduced in patients with
559 hepatic failure. RAXAR Tablets are contraindicated in patients with hepatic failure (see CLINICAL
560 PHARMACOLOGY).

561
562 **HOW SUPPLIED:** RAXAR Tablets 200 mg (grepafloxacin hydrochloride tablets) are supplied as white to
563 pale yellow, film-coated, round, biconvex, bevel-edged tablets containing 200 mg grepafloxacin base. The
564 tablets are imprinted with "GX CK3" on one side and no printing on the other side.

565 60 Tablets/Bottle NDC 0173-0566-03

566 Unit Dose Pack of 60 NDC 0173-0566-00

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(grepafloxacin hydrochloride tablets)

567 RAXAR Tablets 400 mg (grepafloxacin hydrochloride tablets) are supplied as white to pale yellow,
.8 film-coated, oval, biconvex, bevel-edged tablets containing 400 mg grepafloxacin base. The tablets are
569 imprinted with "GX CK5" on one side and no printing on the other side.

570 Unit Dose Pack of 10 (Rax-Pack™ 400) NDC 0173-0657-03

571 RAXAR Tablets 600 mg (grepafloxacin hydrochloride tablets) are supplied as white to pale yellow,
572 film-coated, oval, biconvex, bevel-edged tablets containing 600 mg grepafloxacin base. The tablets are
573 imprinted with "GX CK7" on one side and no printing on the other side.

574 Unit Dose Pack of 10 (Rax-Pack™ 600) NDC 0173-0658-03

575 Store at controlled room temperature of 25°C (77°F) (see United States Pharmacopoeia).

576 Replace cap securely after each opening.

577

578 **CLINICAL STUDIES:**

579 **Acute Bacterial Exacerbations of Chronic Bronchitis:** Two separate controlled, randomized trials of
580 grepafloxacin in the treatment of acute bacterial exacerbations of chronic bronchitis yielded overall
581 efficacy rates of grepafloxacin 400 mg and grepafloxacin 600 mg which demonstrated equivalence to
582 comparators. However, these studies suggest that grepafloxacin 400 mg once daily for 10 days may be
583 less effective against *S. pneumoniae* than grepafloxacin 600 mg once daily for 10 days or comparator for
584 10 days. These studies excluded patients whose respiratory status required the initiation of steroid
585 therapy or an increase in maintenance steroid doses greater than prednisone 10 mg per day (or its
.6 equivalent). Clinical success at end of treatment did not always predict clinical success at follow-up. Table
587 6 presents efficacy data from these two trials at end of treatment (1 to 5 days posttreatment) and at
588 follow-up (14 to 28 days posttreatment).

589

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Table 6: Clinical Efficacy in Studies of Acute Bacterial Exacerbations of Chronic Bronchitis

Study 106-92-301	End of Treatment (1 - 3 Days Posttreatment)			Follow-up (14 Days Posttreatment)		
	Grepafloxacin 400 mg q.d.	Grepafloxacin 600 mg q.d.	Compar- ator	Grepafloxacin 400 mg q.d.	Grepafloxacin 600 mg q.d.	Compar- ator
Overall Efficacy	142/157 (90.4%)	140/150 (93.3%)	152/161 (94.4%)	123/153 (80.4%)	124/149 (83.2%)	137/161 (85.1%)
Efficacy by Individual Organism:						
<i>S. pneumoniae</i>	36/42 (85.7%)	40/41 (97.6%)	43/44 (97.7%)	29/40 (72.5%)	35/41 (85.4%)	38/44 (86.4%)
<i>H. influenzae</i>	63/68 (92.6%)	61/68 (89.7%)	84/90 (93.3%)	55/67 (82.1%)	51/67 (76.1%)	76/90 (84.4%)
<i>M. catarrhalis</i>	41/43 (95.3%)	32/32 (100%)	29/30 (96.7%)	38/42 (90.5%)	31/32 (96.9%)	26/30 (86.7%)

Study 106-92-206	End of Treatment (3 - 5 Days Posttreatment)			Follow-up (14 - 28 Days Posttreatment)		
	Grepafloxacin 400 mg q.d.	Grepafloxacin 600 mg q.d.	Compar- ator	Grepafloxacin 400 mg q.d.	Grepafloxacin 600 mg q.d.	Compar- ator
Overall Efficacy	66/72 (91.7%)	66/71 (93.0%)	65/70 (92.9%)	58/71 (81.7%)	61/71 (85.9%)	54/66 (81.8%)
Efficacy by Individual Organism:						
<i>S. pneumoniae</i>	8/8 (100%)	8/9 (88.9%)	3/5 (60%)	7/8 (87.5%)	6/9 (66.7%)	3/5 (60%)
<i>H. influenzae</i>	18/19 (94.7%)	15/16 (93.8%)	17/18 (94.4%)	17/19 (89.5%)	14/16 (87.5%)	15/18 (83.3%)
<i>M. catarrhalis</i>	20/21 (95.2%)	20/21 (95.2%)	18/19 (94.7%)	19/21 (90.5%)	18/21 (85.7%)	15/16 (93.8%)

Community-acquired Pneumonia: The two pivotal clinical trials that assessed the efficacy of grepafloxacin in the treatment of community-acquired pneumonia excluded patients whose respiratory status required the initiation of steroid therapy or an increase in maintenance steroid doses greater than prednisone 10 mg per day (or its equivalent). Study 106-92-302 was a randomized, controlled study that assessed the efficacy of grepafloxacin 600 mg once daily for 10 days compared with comparator for 10 days. Study 106-92-205 was an open study that assessed clinical efficacy of grepafloxacin 600 mg once daily for 10 days. Table 7 presents efficacy results from the two pivotal studies:

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Table 7: Clinical Efficacy in Community-acquired Pneumonia in Two Pivotal Studies

	Grepafloxacin 600 mg q.d.	Comparator
Study 106-92-302		
Success	89/110 (80.9%)	94/117 (80.3%)
Failure	21/110 (19.1%)	23/117 (19.7%)
Study 106-92-205		
Success	116/125 (92.8%)	
Failure	9/125 (7.2%)	

ANIMAL PHARMACOLOGY: Quinolones have been shown to cause arthropathies in juvenile rats and dogs. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared with the incidence in vehicle-treated rats. Grepafloxacin-associated joint toxicity (cavitation with loss of cartilaginous matrix and chondrocytes with cartilage fibrillation) was observed in juvenile dogs receiving 100 mg/kg by intravenous or subcutaneous injection for 1 week. Grepafloxacin-associated joint toxicity (blisters of the articular cartilage) was observed in juvenile dogs given oral doses of 80 mg/kg per day (approximately 4.3 times the recommended maximum daily human dose on a mg/m² basis) for 4 weeks. No joint toxicity was observed at lower oral doses of 60 mg/kg per day (approximately 3.2 times the recommended maximum daily human dose on a mg/m² basis) for 4 weeks. The clinical relevance of these observations is unknown.

In the dog, oral doses of 30 mg/kg and above (≥ 1.5 times the maximum human dose on a mg/m² basis) caused prolongation of the QT interval, although the results were variable. Intravenous administration of grepafloxacin at 10 mg/kg elicited a moderate hypotension in anesthetized dogs and rabbits.

In phototoxicity tests, mice exposed to ultraviolet A radiation (similar to that used in tanning booths; sunlight contains a wider spectrum of UV radiation) after administration of grepafloxacin as a single 200-mg/kg oral dose (1.6 times the highest recommended human dose, based upon body surface area) showed a mild redness on the ears. Phototoxic reactions such as this have been reported with other quinolones.

Lenticular opacities, sometimes observed after long-term, high-dose use with other quinolones, were not observed with grepafloxacin in a 52-week study in monkeys.

Drug interactions resulting in seizures have been reported between some quinolones and NSAIDs. Grepafloxacin did not induce seizures when administered with a variety of NSAIDs in rats. The NSAIDs studied were fenbufen, flurbiprofen, indomethacin, phenylbutazone, ibuprofen, and diflunisal.

REFERENCES:

RAXAR® Tablets
(grepafloxacin hydrochloride tablets)

- 631 1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial*
632 *Susceptibility Tests for Bacteria that Grow Aerobically*-Fourth Edition. Approved Standard NCCLS
633 Document M7-A4, Volume 17, No. 2, NCCLS, Wayne, PA, January, 1997.
- 634 2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk*
635 *Susceptibility Tests*-Sixth Edition. Approved Standard NCCLS Document M2-A6, Volume 17, No. 1.
636 NCCLS, Wayne, PA, January, 1997.

637

638 **GlaxoWellcome**

639 Glaxo Wellcome Inc.

640 Research Triangle Park, NC 27709

641

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643

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