CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 065156Orig1s010

Name: Minocycline Hydrochloride Tablets USP 50 mg, 75 mg, and 100 mg

Sponsor: Ranbaxy, Inc.

Approval Date: May 11, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065156Orig1s010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065156s010

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20855

ANDA 065156/S-010

Ranbaxy, Inc.
Attention: Manisha Sharma
Senior Regulatory Associate
600 College Road East
Princeton, NJ 08540

Dear Madam:

Please refer to your supplemental new drug application dated December 22, 2010, submitted pursuant to 21 CFR 314.70(c) (6) [Supplement – Changes Being Effected] regarding your abbreviated new drug application for Minocycline Hydrochloride Tablets USP, 50 mg, 75 mg, and 100 mg.

Reference is also made to our letter dated July 13, 2011, and your amendment dated October 5, 2011.

This supplemental new drug application provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert.

We have completed the review of your application as amended and it is approved. However, further revise your insert labeling as follows at the time of next printing:

PROFESSIONAL PACKAGE INSERT

CLINICAL PHARMACOLOGY

a. 2nd paragraph - Please include "Minocycline hydrochloride tablets may be administered with or without food." to appear at the end of the paragraph.

b. Please decrease the prominence of "Ref1, Ref2, etc" through the use of superscript.

c. Susceptibility Tests, Diffusion Techniques - Table immediately prior to the title, INDICATIONS AND USAGE – 4th row

We note that there is an error in the innovator drug labeling, Minocin®, NDA 50649/S-023. Please revise "*Staphylococcus aureus* ATCC 29213" to read "*Staphylococcus aureus* ATCC 25923"

DOSAGE AND ADMINISTRATION – 3rd paragraph

Please include "The tablets should be swallowed whole." to appear at the end of the paragraph.

REFERENCES

Ref2 – 2nd line

Revise to read "…for Antimicrobial Disk Susceptibility Tests…" [Note; "Disk" Rather than "Disks"]

PATIENT INFORMATION LEAFLET

Please include disclaimers for Accutane®, Amnesteem®, Claravis®, and Sotret®.

Revised labeling may be submitted in an annual report provided all the changes are described in full.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The materials submitted are being retained in our files.

Sincerely,

{See appended electronic signature page}
William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LILLIE D GOLSON
05/11/2012
for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065156s010

LABELING

MINOCYCLINE HYDROCHLORIDE TABLETS, USP
Rx only

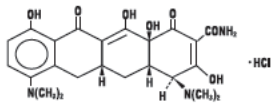
MINOCYCLINE HYDROCHLORIDE TABLETS, USP
Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of minocycline hydrochloride tablets, USP and other antibacterial drugs, minocycline hydrochloride tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Minocycline hydrochloride, USP is a semisynthetic derivative of tetracycline, 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride.

Its structural formula is:



$C_{22}H_{27}N_3O_7 \cdot HCl$ M.W. 493.94

Minocycline hydrochloride tablets, USP for oral administration, contains minocycline hydrochloride, USP equivalent to 50 mg, 75 mg or 100 mg of minocycline. In addition, each film-coated tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, polyethylene glycol 6000, silicified microcrystalline cellulose, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Following a single dose of one 100 mg tablet of minocycline hydrochloride administered to 28 normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 3 hours (average 1.71 hours) and ranged from 491.71 to 1292.70 ng/mL (average 758.29 ng/mL). The serum half-life in the normal volunteers ranged from 11.38 to 24.31 hours (average 17.03 hours).

When minocycline hydrochloride tablets were given concomitantly with a meal, which included dairy products, the extent of absorption of minocycline hydrochloride tablets was slightly decreased (6%). The peak plasma concentrations were slightly decreased (12%) and delayed by 1.09 hours when administered with food, compared to dosing under fasting conditions.

In previous studies with other minocycline dosage forms, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers was one-half to one-third that of other tetracyclines.

Microbiology

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracycline is common.

Minocycline 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
Because many strains of the following gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Tetracycline antibiotics should not be used for streptococcal diseases unless the organism has been demonstrated to be susceptible. Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.
Bacillus anthracis[1]
Listeria monocytogenes[1]
Staphylococcus aureus
Streptococcus pneumoniae
AEROBIC GRAM-NEGATIVE MICROORGANISMS
Bartonella bacilliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Vibrio cholerae
Yersinia pestis
Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended.
Acinetobacter species
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella species
Neisseria gonorrhoeae[1]
Neisseria meningitidis[1]
Shigella species
"OTHER" MICROORGANISMS
Actinomyces species[1]
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species[1]
Entamoeba species
Fusobacterium nucleatum subspecies *fusiforme*[1]
Mycobacterium marinum
Mycoplasma pneumoniae
Propionibacterium acnes
Rickettsiae
Treponema pallidum subspecies *pallidum*[1]
Treponema pallidum subspecies *pertenue*[1]
Ureaplasma urealyticum

[1] When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections caused by the cited microorganisms.

Susceptibility Tests

Susceptibility testing should be performed with tetracycline since it predicts susceptibility to minocycline. However, certain organisms (e.g., some staphylococci and *Acinetobacter* species) may be more susceptible to minocycline and doxycycline than to tetracycline.

Dilution techniques:
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (Ref1, Ref3) (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of tetracycline powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus*:

MIC (mcg/mL)	Interpretation
≤ 4	Susceptible (S)
8	Intermediate (I)
≥ 16	Resistant (R)

For testing *Haemophilus influenzae*[2] and *Streptococcus pneumoniae*[3]:

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

[2] These interpretative standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium.Ref1

[3] These interpretative standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Muller-Hinton broth with 2 to 5% lysed horse blood.[1]

For testing *Neisseria gonorrhoeae*[4]:

MIC (mcg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5 to 1	Intermediate (I)
≥ 2	Resistant (R)

[4] These interpretative standards are applicable only to agar dilution susceptibility testing using GC agar base and 1% defined growth supplements.Ref1

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations 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 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 concentrations 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 tetracycline powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL)
Escherichia coli ATCC 25922	0.5 to 2
Enterococcus faecalis ATCC 29212	8 to 32
Staphylococcus aureus ATCC 29213	0.25 to 1
Haemophilus influenzae ATCC 49247	4 to 32
Streptococcus pneumoniae ATCC 49619	0.12 to 0.5
Neisseria gonorrhoeae ATCC 49226	0.25 to 1

Diffusion techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (Ref2, Ref3) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg tetracycline (class disk) or 30 mcg minocycline to test the susceptibility of microorganisms to minocycline.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg tetracycline or minocycline disk should be interpreted according to the following criteria:

For testing aerobic gram-negative microorganisms (Enterobacteriaceae), *Acinetobacter* species and *Staphylococcus aureus:*

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
15 to 18	Intermediate (I)
≤ 14	Resistant (R)

For testing *Haemophilus influenzae*[5]:

Zone Diameter (mm)	Interpretation
≥ 29	Susceptible (S)
26 to 28	Intermediate (I)
≤ 25	Resistant (R)

[5] These zone diameter standards are applicable only to susceptibility testing with *Haemophilus influenzae* using Haemophilus Test Medium and a 30 mcg tetracycline disk.Ref2

For testing *Neisseria gonorrhoeae*[6]:

Zone Diameter (mm)	Interpretation
≥ 38	Susceptible (S)
31 to 37	Intermediate (I)
≤ 30	Resistant (R)

[6] These interpretative standards are applicable only to disk diffusion testing using GC agar and 1% growth supplements, and a 30 mcg tetracycline disk.Ref2

For testing *Streptococcus pneumoniae*[7]:

Zone Diameter (mm)	Interpretation
≥ 23	Susceptible (S)
19 to 22	Intermediate (I)
≤ 18	Resistant (R)

[7] These interpretative standards are applicable only to disk diffusion testing using Muller-Hinton agar adjusted with 5% sheep blood and a 30 mcg tetracycline disk.Ref2

For testing *Vibrio cholerae*[8]:

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
15 to 18	Intermediate (I)
≤ 14	Resistant (R)

[8] These interpretative standards are applicable only to disk diffusion testing performed with a 30 mcg tetracycline disk.(Ref2)

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 tetracycline.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg tetracycline or minocycline disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter Range (mm)	
	Tetracycline	Minocycline
Escherichia coli ATCC 25922	18 to 25	19 to 25
Staphylococcus aureus ATCC 29213	24 to 30	25 to 30
Haemophilus influenzae ATCC 49247	14 to 22	-
Neisseria gonorrhoeae ATCC 49226	30 to 42	-
Streptococcus pneumoniae ATCC 49619	27 to 31	-

INDICATIONS AND USAGE

Minocycline hydrochloride tablets, USP are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:
Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by rickettsiae.
Respiratory tract infections caused by *Mycoplasma pneumoniae.*
Lymphogranuloma venereum caused by *Chlamydia trachomatis.*
Psittacosis (Ornithosis) due to *Chlamydia psittaci.*
Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.
Inclusion conjunctivitis caused by *Chlamydia trachomatis.*
Nongonococcal urethritis, endocervical, or rectal infections in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis.*
Relapsing fever due to *Borrelia recurrentis.*
Chancroid caused by *Haemophilus ducreyi.*
Plague due to *Yersinia pestis.*
Tularemia due to *Francisella tularensis.*
Cholera caused by *Vibrio cholerae.*
Campylobacter fetus infections caused by *Campylobacter fetus.*
Brucellosis due to *Brucella* species (in conjunction with streptomycin).
Bartonellosis due to *Bartonella bacilliformis.*
Granuloma inguinale caused by *Calymmatobacterium granulomatis.*
Minocycline is indicated for the treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
Escherichia coli.
Enterobacter aerogenes.
Shigella species.
Acinetobacter species.
Respiratory tract infections caused by *Haemophilus influenzae.*
Respiratory tract and urinary tract infections caused by *Klebsiella* species.
Minocycline hydrochloride tablets, USP are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
Upper respiratory tract infections caused by *Streptococcus pneumoniae.*
Skin and skin structure infections caused by *Staphylococcus aureus* (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection).
When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:
Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections.
Infections in women caused by *Neisseria gonorrhoeae.*
Syphilis caused by *Treponema pallidum* subspecies *pallidum.*
Yaws caused by *Treponema pallidum* subspecies *pertenue.*
Listeriosis due to *Listeria monocytogenes.*
Anthrax due to *Bacillus anthracis.*
Vincent's infection caused by *Fusobacterium fusiforme.*
Actinomycosis caused by *Actinomyces israelli.*
Infections caused by *Clostridium* species.
In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.
In severe *acne*, minocycline may be useful adjunctive therapy.
Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.
Oral minocycline is not indicated for the treatment of meningococcal infection.
Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum.*
To reduce the development of drug-resistant bacteria and maintain the effectiveness of minocycline hydrochloride tablets, USP and other antibacterial drugs, minocycline hydrochloride tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or to any of the components of the product formulation.

WARNINGS

MINOCYCLINE HYDROCHLORIDE, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. **TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.**

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

PATIENT INFORMATION
MINOCYCLINE HYDROCHLORIDE TABLETS, USP
Rx only

Read the Patient Information that comes with minocycline hydrochloride tablets, USP before you or a family member starts taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

What are minocycline hydrochloride tablets, USP?

Minocycline hydrochloride tablets, USP are a tetracycline-class antibiotic medicine. Minocycline hydrochloride tablets, USP are used to treat certain infections caused by bacteria. These include infections of the skin, respiratory tract, urinary tract, some sexually transmitted diseases, and others. Minocycline hydrochloride tablets, USP may be used along with other treatments for severe acne.

Sometimes, other germs, called viruses cause infections. The common cold is a virus. Minocycline hydrochloride tablets, USP, like other antibiotics, does not treat viruses.

Who should not use minocycline hydrochloride tablets, USP?

Do not take minocycline hydrochloride tablets, USP if you are allergic to minocycline or other tetracycline antibiotics.

Ask your doctor or pharmacist for a list of these medications if you are not sure. See the end of this leaflet for a complete list of ingredients in minocycline hydrochloride tablets, USP.

Minocycline hydrochloride tablets, USP are not recommended for pregnant women or children up to 8 years old because:

1. **Minocycline hydrochloride tablets, USP may harm an unborn baby**
2. **Minocycline hydrochloride tablets, USP may permanently turn a baby's or child's teeth yellow-gray-brown during tooth development.** Tooth development happens in the last half of pregnancy and birth to age 8 years.

What should I tell my doctor before starting minocycline hydrochloride tablets, USP?

Tell your doctor about all of your medical conditions, including if you:

- **have liver or kidney problems**
- **are pregnant or planning to become pregnant.** Minocycline hydrochloride tablets, USP may harm your unborn baby. **Stop taking minocycline hydrochloride tablets, USP and call your doctor if you become pregnant while taking it.**
- **are breast feeding.** Minocycline passes into your milk and may harm your baby. You should decide whether to use minocycline hydrochloride tablets, USP or breastfeed, but not both.

Tell your doctor about all the medicines you are taking including prescription and non-prescription medications, vitamins, and herbal supplements. Minocycline hydrochloride tablets, USP and other medicines may interact. Especially tell your doctor if you take:

- **birth control pills.** Minocycline hydrochloride tablets, USP may make your birth control pills less effective
- **a blood thinner medicine.** The dose of your blood thinner may have to be lowered.
- **a penicillin antibiotic medicine.** Minocycline hydrochloride tablets, USP and penicillins should not be used together.
- **Migraine medicines called ergot alkaloids.**
- **An acne medicine called isotretinoin (Accutane, Amnesteem, Claravis, Sotret).**
- **Antacids that contain aluminum, calcium, or magnesium, or iron-containing products.**

Know the medicines you take, keep a list of them to show your doctor and pharmacist each time you get a new medicine.

How should I take minocycline hydrochloride tablets, USP?

- **Take minocycline hydrochloride tablets, USP exactly as your doctor tells you to take them.** Skipping doses or not taking all your minocycline hydrochloride tablets, USP may:
  - Decrease the effectiveness of the treatment.
  - Increase the chance that bacteria will develop resistance to minocycline hydrochloride tablets, USP.
- **Take minocycline hydrochloride tablets, USP with a full glass of liquid.** Taking minocycline hydrochloride tablets, USP with enough

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Track: A30/08/2011-II, A15/09/2011

liquid may lower your chance of getting irritation or ulcers in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.

- **Minocycline hydrochloride tablets, USP** may be taken with or without food. If you forget to take minocycline hydrochloride tablets, USP, take it as soon as you remember.
- If you take too much minocycline hydrochloride tablets, USP, call your doctor or poison control center right away.

What are the possible side effects of minocycline hydrochloride tablets, USP?

Minocycline hydrochloride tablets, USP may cause serious side effects. Stop minocycline hydrochloride tablets, USP and call your doctor if you have:

- watery diarrhea
- bloody stools
- stomach cramps
- unusual headaches
- blurred vision
- fever
- rash
- joint pain
- feeling very tired

Minocycline hydrochloride tablets, USP may also cause:

- **central nervous system effects**. Symptoms include light-headedness, dizziness, and a spinning feeling (vertigo). You should not drive or operate machines if you have these symptoms.
- **sun sensitivity (photosensitivity)**. You may get a worse sunburn with minocycline hydrochloride tablets, USP. Avoid sun exposure and the use of sunlamps or tanning beds. Protect your skin while out in the sunlight. Stop minocycline hydrochloride tablets, USP and call your doctor if your skin turns red.

These are not all the side effects with minocycline hydrochloride tablets, USP. Ask your doctor or pharmacist for more information.

How should I store minocycline hydrochloride tablets, USP?

- Store minocycline hydrochloride tablets, USP at room temperature and away from excess heat and moisture.
- Throw away any minocycline hydrochloride tablets, USP that is outdated or no longer needed.
- **Keep minocycline hydrochloride tablets, USP and all medicines out of the reach of children.**

General advice about minocycline hydrochloride tablets, USP

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use minocycline hydrochloride tablets, USP for a condition for which it was not prescribed. Do not give minocycline hydrochloride tablets, USP to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about minocycline hydrochloride tablets, USP. If you would like more information, talk with your doctor.

Your doctor or pharmacist can give you information about minocycline hydrochloride tablets, USP that is written for health care professionals. For more information, you can also call Ranbaxy Pharmaceuticals Inc. at 1-800-406-7984.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088**.

What are the ingredients in minocycline hydrochloride tablets, USP?

Active ingredient: minocycline hydrochloride, USP, 50 mg, 75 mg and 100 mg

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, polyethylene glycol 6000, silicified microcrystalline cellulose, stearic acid, and titanium dioxide.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA

September 2011 FDA-05

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. Under such conditions, monitoring of creatinine and BUN is recommended, and the total daily dosage should not exceed 200 mg in 24 hours (see **DOSAGE AND ADMINISTRATION**). If renal impairment exists, even usual oral or parenteral doses may lead to systemic accumulation of the drug and possible liver toxicity.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported with minocycline.

Central nervous system side effects including light-headedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including minocycline hydrochloride, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Hepatotoxicity has been reported with minocycline; therefore, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Prescribing minocycline hydrochloride tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information For Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. This reaction has been reported with use of minocycline.

Patients who experience central nervous system symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy (see **WARNINGS**).

Concurrent use of tetracycline with oral contraceptives may render oral contraceptives less effective (see **Drug Interactions**).

Patients should be counseled that antibacterial drugs including minocycline hydrochloride tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When minocycline hydrochloride tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by minocycline hydrochloride tablets or other antibacterial drugs in the future.

Unused supplies of tetracycline antibiotics should be discarded by the expiration date.

Laboratory Tests

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

Periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic, should be performed.

Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

Administration of isotretinoin should be avoided shortly before, during, and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri (see **PRECAUTIONS**).

Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary administration of minocycline in long term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in *in vitro* mammalian cell assays (i.e., mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rats.

Pregnancy

Teratogenic Effects: Pregnancy Category D (see **WARNINGS**).

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class antibiotics, crosses the placenta and may cause fetal harm when administered to a pregnant woman. Rare spontaneous reports of congenital anomalies including limb reduction have been reported in postmarketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established. If minocycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nonteratogenic Effects: (see **WARNINGS**).

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see **WARNINGS**).

Pediatric Use

Minocycline is not recommended for the use in children below 8 years of age unless the expected benefits of therapy outweigh the risks (see **WARNINGS**).

Geriatric Use

Clinical studies of oral minocycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **WARNINGS, DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Body as a whole: Fever, and discoloration of secretions.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, dyspepsia, stomatitis, glossitis, dysphagia, enamel hypoplasia, enterocolitis, pseudomembranous colitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the oral and anogenital regions. Instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see **DOSAGE AND ADMINISTRATION**).

Genitourinary: Vulvovaginitis.

Hepatic toxicity: Hyperbilirubinemia, hepatic cholestasis, increases in liver enzymes, fatal hepatic failure, and jaundice. Hepatitis, including autoimmune hepatitis, and liver failure have been reported (see **PRECAUTIONS**).

Skin: Alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, and vasculitis. Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported. Fixed drug eruptions have been reported. Lesions occurring on the glans penis have caused balanitis. Erythema multiforme and Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see **WARNINGS**). Pigmentation of the skin and mucous membranes has been reported.

Respiratory: Cough, dyspnea, bronchospasm, exacerbation of asthma, and pneumonitis.

Renal toxicity: Interstitial nephritis. Elevations in BUN have been reported and are apparently dose related (see **WARNINGS**). Reversible acute renal failure has been reported.

Musculoskeletal: Arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling.

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis/anaphylactoid reaction (including shock and fatalities), anaphylactoid purpura, myocarditis, pericarditis, exacerbation of systemic lupus erythematosus and pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome and serum sickness-like reactions also have been reported.

Blood: Agranulocytosis, hemolytic anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, and eosinophilia have been reported.

Central Nervous System: Convulsions, dizziness, hypesthesia, paresthesia, sedation, and vertigo. Bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults have been reported (see **PRECAUTIONS - General**). Headache has also been reported.

Other: Thyroid cancer has been reported in the postmarketing setting in association with minocycline products. When minocycline therapy is given over prolonged periods, monitoring for signs of thyroid cancer should be considered. When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. Cases of abnormal thyroid function have been reported.

Tooth discoloration in children less than 8 years of age (see **WARNINGS**) and also, in adults has been reported.

Oral cavity discoloration (including tongue, lip, and gum) have been reported.

Tinnitus and decreased hearing have been reported in patients on minocycline hydrochloride.

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognized, the drug should be discontinued immediately:

Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present.

Lupus-like syndrome consisting of positive antinuclear antibody; arthralgia, arthritis, joint stiffness, or joint swelling; and one or more of the following: fever, myalgia, hepatitis, rash, and vasculitis.

Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness, or joint swelling. Eosinophilia may be present.

OVERDOSAGE

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting.

No specific antidote for minocycline is known.

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride tablets may be taken with or without food (see **CLINICAL PHARMACOLOGY**).

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

For Pediatric Patients Above 8 Years Of Age

Usual pediatric dose: 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose.

Adults

The usual dosage of minocycline hydrochloride tablets is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg tablets may be given initially followed by one 50 mg tablet 4 times daily.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of 4 days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for 5 days is recommended.

For the treatment of syphilis, the usual dosage of minocycline hydrochloride should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for 5 days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg orally, every 12 hours for at least 7 days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

The pharmacokinetics of minocycline in patients with renal impairment (CL_{CR} < 80 mL/min) have not been fully characterized. Current data are insufficient to determine if a dosage adjustment is warranted. The total daily dosage should not exceed 200 mg in 24 hours. However, due to the anti-anabolic effect of tetracyclines, BUN and creatinine should be monitored (see **WARNINGS**).

HOW SUPPLIED

Minocycline hydrochloride tablets, USP equivalent to 50 mg minocycline are yellow colored, oval-shaped, film-coated tablets, debossed with **"RI89"** on one side and plain on the other side. They are supplied as follows:

NDC 63304-697-01	Bottles of 100
NDC 63304-697-05	Bottles of 500

Minocycline hydrochloride tablets, USP equivalent to 75 mg minocycline are yellow colored, oval-shaped, film-coated tablets, debossed with **"RI90"** on one side and plain on the other side. They are supplied as follows:

NDC 63304-698-01	Bottles of 100
NDC 63304-698-05	Bottles of 500

Minocycline hydrochloride tablets, USP equivalent to 100 mg minocycline are yellow colored, oval-shaped, film-coated tablets, debossed with **"RI91"** on one side and plain on the other side. They are supplied as follows:

NDC 63304-699-50	Bottles of 50
NDC 63304-699-05	Bottles of 500

Store at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature].
Protect from light, moisture, and excessive heat.
Dispense in a tight, light-resistant container as defined in the USP.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline hydrochloride has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

REFERENCES

Ref1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fourth Edition; Approved Standard. NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disks Susceptibility Tests—Sixth Edition; Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1997.

Ref3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Testing—Eighth Edition; Approved Standard NCCLS Document M100-S8, Vol.18, No.1, NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA, January 1998.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA

September 2011 FDA-05

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PATIENT INFORMATION

MINOCYCLINE HYDROCHLORIDE TABLETS, USP

Rx only

Read the Patient Information that comes with minocycline hydrochloride tablets, USP before you or a family member starts taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

What are minocycline hydrochloride tablets, USP?

Minocycline hydrochloride tablets, USP are a tetracycline-class antibiotic medicine. Minocycline hydrochloride tablets, USP are used to treat certain infections caused by bacteria. These include infections of the skin, respiratory tract, urinary tract, some sexually transmitted diseases, and others. Minocycline hydrochloride tablets, USP may be used along with other treatments for severe acne.

Sometimes, other germs, called viruses cause infections. The common cold is a virus. Minocycline hydrochloride tablets, USP, like other antibiotics, does not treat viruses.

Who should not use minocycline hydrochloride tablets, USP?

Do not take minocycline hydrochloride tablets, USP if you are allergic to minocycline or other tetracycline antibiotics.

Ask your doctor or pharmacist for a list of these medications if you are not sure. See the end of this leaflet for a complete list of ingredients in minocycline hydrochloride tablets, USP.

Minocycline hydrochloride tablets, USP are not recommended for pregnant women or children up to 8 years old because:

1. **Minocycline hydrochloride tablets, USP may harm an unborn baby**
2. **Minocycline hydrochloride tablets, USP may permanently turn a baby's or child's teeth yellow-gray-brown during tooth development**. Tooth development happens in the last half of pregnancy and birth to age 8 year.

What should I tell my doctor before starting minocycline hydrochloride tablets, USP?

Tell your doctor about all of your medical conditions, including if you:

- **have liver or kidney problems**
- **are pregnant or planning to become pregnant**. Minocycline hydrochloride tablets, USP may harm your unborn baby. **Stop taking minocycline hydrochloride tablets, USP and call your doctor if you become pregnant while taking it.**
- **are breast feeding**. Minocycline passes into your milk and may harm your baby. You should decide whether to use minocycline hydrochloride tablets, USP or breastfeed, but not both.

Tell your doctor about all the medicines you are taking including prescription and non-prescription medications, vitamins, and herbal supplements. Minocycline hydrochloride tablets, USP and other medicines may interact. Especially tell your doctor if you take:

- **birth control pills.** Minocycline hydrochloride tablets, USP may make your birth control pills less effective
- **a blood thinner medicine.** The dose of your blood thinner may have to be lowered.
- **a penicillin antibiotic medicine**. Minocycline hydrochloride tablets, USP and penicillins should not be used together.
- **Migraine medicines called ergot alkaloids.**
- **An acne medicine called isotretinoin (Accutane, Amnesteem, Claravis, Sotret).**
- **Antacids that contain aluminum, calcium, or magnesium, or iron-containing products.**

Know the medicines you take, keep a list of them to show your doctor and pharmacist each time you get a new medicine.

How should I take minocycline hydrochloride tablets, USP?

- **Take minocycline hydrochloride tablets, USP exactly as your doctor tells you to take them.** Skipping doses or not taking all your minocycline hydrochloride tablets, USP may:
  - Decrease the effectiveness of the treatment.
  - Increase the chance that bacteria will develop resistance to minocycline hydrochloride tablets, USP.
- **Take minocycline hydrochloride tablets, USP with a full glass of liquid.** Taking minocycline hydrochloride tablets, USP with enough liquid may lower your chance of getting irritation or ulcers in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.
- Minocycline hydrochloride tablets, USP may be taken with or without food. If you forget to take minocycline hydrochloride tablets, USP, take it as soon as you remember.

- If you take too much minocycline hydrochloride tablets, USP, call your doctor or poison control center right away.

What are the possible side effects of minocycline hydrochloride tablets, USP?

Minocycline hydrochloride tablets, USP may cause serious side effects. Stop minocycline hydrochloride tablets, USP and call your doctor if you have:

- watery diarrhea
- bloody stools
- stomach cramps
- unusual headaches
- blurred vision
- fever
- rash
- joint pain
- feeling very tired

Minocycline hydrochloride tablets, USP may also cause:

- **central nervous system effects**. Symptoms include light-headedness, dizziness, and a spinning feeling (vertigo). You should not drive or operate machines if you have these symptoms.
- **sun sensitivity (photosensitivity)**. You may get a worse sunburn with minocycline hydrochloride tablets, USP. Avoid sun exposure and the use of sunlamps or tanning beds. Protect your skin while out in the sunlight. Stop minocycline hydrochloride tablets, USP and call your doctor if your skin turns red.

These are not all the side effects with minocycline hydrochloride tablets, USP. Ask your doctor or pharmacist for more information.

How should I store minocycline hydrochloride tablets, USP?

- Store minocycline hydrochloride tablets, USP at room temperature and away from excess heat and moisture.
- Throw away any minocycline hydrochloride tablets, USP that is outdated or no longer needed.
- **Keep minocycline hydrochloride tablets, USP and all medicines out of the reach of children.**

General advice about minocycline hydrochloride tablets, USP

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use minocycline hydrochloride tablets, USP for a condition for which it was not prescribed. Do not give minocycline hydrochloride tablets, USP to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about minocycline hydrochloride tablets, USP. If you would like more information, talk with your doctor.

Your doctor or pharmacist can give you information about minocycline hydrochloride tablets, USP that is written for health care professionals. For more information, you can also call Ranbaxy Pharmaceuticals Inc. at 1-800-406-7984.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088**.

What are the ingredients in minocycline hydrochloride tablets, USP?

Active ingredient: minocycline hydrochloride, USP, 50 mg, 75 mg and 100 mg

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, polyethylene glycol 6000, silicified microcrystalline cellulose, stearic acid, and titanium dioxide.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA

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September 2011 FDA-05

PIL Size : 150 x 300 mm
Font Size : 10 Pt.
Color : Black
Track : A22/09/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065156s010

LABELING REVIEWS

(COMPLETE RESPONSE)
Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs
Labeling Supplement Review

Application Number: 065156/S-010

Name of Drug: Minocycline Hydrochloride Tablets USP, 50 mg, 75 mg, and 100 mg

Applicant: Ranbaxy Laboratories Limited

Material Reviewed: (specify labeling pieces)

CBE submission: Revised package insert labeling (FPL and SPL), PPI, and container labels

Submission Date(s): December 22, 2010 and June 21, 2011

Date of Review: July 5, 2011

Background and Summary

1. **This supplemental new drug application provides for:**

The supplemental application dated December 22, 2010 provides

- Revisions to the insert in accordance with the innovator drug, Minocin® Pellet-Filled Capsule, (NDA 50649/S-023), approved September 14, 2010
- Minor revisions to the container labels regarding Usual Dosage information

The supplemental application dated June 21, 2011 is to amend the CBE Labeling supplement submitted on December 22, 2010 to correct the imprinting of the tablets in the HOW SUPPLIED section of the FPL and the data elements section of the SPL.

2. **Model labeling: (include name, application number and date approved):**

- The innovator labeling, Minocin® Pellet-Filled Capsules (NDA 50649/S-023) by Triax Pharms LLC was approved September 14, 2010.
- The last approved labeling for this ANDA was used for the DESCRIPTION and the HOW SUPPLIED sections. There are changes in the imprinting of the tablets, packaging configurations, and the scoring configuration for the 100 mg tablets in the HOW SUPPLIED section. See comment below.
- Medicis' ANDA 65-131 is the RLD for the oral tablet dosage form of minocycline (Per Electronic Orange Book). Suitability Petition for the tablet dosage form was approved November 30, 1998. The labeling contains CLINICAL PHARMACOLOGY section specific for the dosage form.

3. Patent/Exclusivity Statement:

None

4. USP 34: May 1, 2011

Packaging and storage— Preserve in tight, light-resistant containers.

Recommendation

1. GENERAL

We note that you revised the [redacted] (b) (4) from the one approved by the Agency (S-008 approved October 27, 2008). We are not able to approve the labeling until the revised [redacted] (b) (4) are found acceptable. Please submit the CMC information associated with these changes and/or comment.

2. CONTAINER: 100s and 500s for 50 mg and 75 mg, and 50s and 500s for 100 mg

Please revise storage recommendations to read "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. [Note; "20°" rather than "20" and "68°" rather than "68"]

3. PROFESSIONAL INSERT:

a. CLINICAL PHARMACOLOGY

Please note that the RLD, ANDA 65131, by Medicis Pharmaceutical Corporation has CLINICAL PHARMACOLOGY section specific for the tablet dosage form. Revise accordingly. Please contact Soon Oh (Soon.Oh@fda.hhs.gov) for the RLD labeling.

"CLINICAL PHARMACOLOGY

Following a single dose of one 100 mg tablet of minocycline hydrochloride administered to 28 normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 3 hours (average 1.71 hours) and ranged from 491.71 to 1292.70 ng/mL (average 758.29 ng/mL). The serum half-life in the normal volunteers ranged from 11.38 to 24.31 hours (average 17.03 hours).

When minocycline hydrochloride tablets were given concomitantly with a meal, which included dairy products, the extent of absorption of minocycline hydrochloride tablets was slightly decreased (6%). The peak plasma concentrations were slightly decreased (12%) and delayed by 1.09 hours when administered with food, compared to dosing under fasting conditions.

In previous studies with other minocycline dosage forms, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers was one-half to one-third that of other tetracyclines."

b. HOW SUPPLIED

i. See comments under GENERAL

ii. See comment under CONTAINER

iii. We note that the [redacted] (b) (4) for the 100 mg tablets is not consistent with the one in the previous package insert. Please clarify and/or comment.

iv. Revise to read "Dispense in a tight, light resistant container as defined in the USP." or "Dispense in tight, light resistant containers as defined in the USP."

c. REFERENCES

i. Ref 1, 4th line – Revise to read "…, Suite 1400, Wayne, PA, January 1997." [Note; comma included after "Wayne"]

ii. Ref 2, 4th line – Revise to read "…1400, Wayne, PA…" [Note; comma included after "1400"]

iii. Ref 4, 3rd and 4th line – Revise to read "…940 West Valley Road, Suite 1400, Wayne, PA…" [Note; comma included after "Road", "1400", and "Wayne"]

4. SPL - DATA ELEMENTS

Active Ingredient/Active Moiety – Basis of Strength

Please note that the strength of your drug product is based on "minocycline" rather than "minocycline hydrochloride". Revise accordingly.

5. PATIENT INFORMATION LEAFLET

Satisfactory in FPL as of the December 22, 2010 submission.

{see appended electronic signature}

(Soon Oh)
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

(Lillie Golson)
Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOON M OH
07/12/2011

LILLIE D GOLSON
07/13/2011

(APPROVAL)
Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs
Labeling Supplement Review

Application Number: 065156/S-010

Name of Drug: Minocycline Hydrochloride Tablets USP, 50 mg, 75 mg, and 100 mg

Applicant: Ranbaxy Laboratories Limited

Material Reviewed: (specify labeling pieces)

CBE submission: Revised package insert labeling (FPL and SPL), and PPI

Submission Date(s): October 5, 2011 (amendment)

Date of Review: May 8, 2012

Background and Summary

1. **This supplemental new drug application provides for:**

   Revisions to the insert in response to the Complete Response letter dated July 13, 2011

2. **This supplement is not combined with chemistry.**

3. **Model labeling: (include name, application number and date approved):**

   - The innovator labeling, Minocin® Pellet-Filled Capsules (NDA 50649/S-023) by Triax Pharms LLC was approved September 14, 2010.

   - Dynacin® (Minocycline Hydrochloride Tablets, USP), ANDA 65-131, by Par Pharmaceuticals, Inc. is the RLD for the oral tablet dosage form of minocycline (Per Electronic Orange Book). Suitability Petition for the tablet dosage form was approved November 30, 1998. The labeling contains CLINICAL PHARMACOLOGY section specific for the dosage form.

4. Patent/Exclusivity Statement: None

5. USP: Yes (checked May 8, 2011)

   Packaging and storage— Preserve in tight, light-resistant containers.

6. PF – No (checked May 8, 2011)

7. The firm is not [redacted] (b) (4)

8. The firm revised the imprinting and filed in the annual report period of February 1, 2009 through January 31, 2010. See the response letter from the firm below.

During the Annual Reporting period February 1, 2009 through January 31, 2010, the debossing code was revised as follows:
50 mg: yellow colored, oval-shaped, film-coated tablets, debossed with **"RI89"** on one side and plain on other side.
75 mg: yellow colored, oval-shaped, film-coated tablets, debossed with **"RI90"** on one side and plain on other side.
100 mg: yellow colored, oval-shaped, film-coated tablets, debossed with **"RI91"** on one side and plain on other side.
Please note, as per the Agency's guidance on "Changes to ANDA/NDA", the changes mentioned above are considered annual reportable changes. Based on this, the CMC information related to the change in the debossing code was filed in the annual report period of February 1, 2009 through January 31, 2010. The labeling provided in this submission reflects the revised description of the tablets.

9. The Table immediately prior to the title, INDICATIONS AND USAGE – 4th row should read "*Staphylococcus aureus* ATCC 25923" rather than "*Staphylococcus aureus* ATCC 29213". See email below from OND.

From: Marsik, Frederic J
Sent: Tuesday, May 08, 2012 12:11 PM
To: Oh, Soon
Cc: Nambiar, Sumathi; Dillon Parker, Maureen P
Subject: FW: Minocin, NDA 50649/S-023, labeling

There is an error in the Minocin PI (NDA 50649). It should be *S. aureus* ATCC 25923 not 29213. *S aureus* ATCC 29213 is used for MIC testing and *S. aureus* ATCC 25923 is used for disc diffusion testing.

Fred

From: Oh, Soon
Sent: Tuesday, May 08, 2012 11:26 AM
To: Nambiar, Sumathi
Subject: Minocin, NDA 50649/S-023, labeling

Hi Dr. Nambiar,

Can you please clarify the table immediately prior to the title, INDICATIONS AND USAGE for me? On the second line, is *Staphylococcus aureus* ATCC 25923 the correct statement or *Staphylococcus aureus* ATCC 29213?
I find ATCC 25923 in the labeling the firm submitted for the supplement 023 and in the labeling of supplement 022. However, I find ATCC 29213 in the labeling that was attached to the approval letter and in the Drugs@FDA website.

Recommendation

1. PROFESSIONAL PACKAGE INSERT

CLINICAL PHARMACOLOGY

a. 2nd paragraph - Please include "Minocycline hydrochloride tablets may be administered with or without food." to appear at the end of the paragraph.

b. Please decrease the prominence of “Ref1, Ref2, etc” through the use of superscript.

c. Susceptibility Tests, Diffusion Techniques - Table immediately prior to the title, INDICATIONS AND USAGE – 4th row

We note that there is an error in the innovator drug labeling, Minocin®, NDA 50649/S-023. Please revise “*Staphylococcus aureus* ATCC 29213” to read “*Staphylococcus aureus* ATCC 25923”

DOSAGE AND ADMINISTRATION – 3rd paragraph

Please include “The tablets should be swallowed whole.” to appear at the end of the paragraph.

REFERENCES

Ref2 – 2nd line

Revise to read “…for Antimicrobial Disk Susceptibility Tests…” [Note; “Disk” Rather than “Disks”]

2. SPL - DATA ELEMENTS

Satisfactory in FPL as of the October 5, 2011 submission.

3. PATIENT INFORMATION LEAFLET

Please include disclaimers for Accutane®, Amnesteem®, Claravis®, and Sotret®.

{see appended electronic signature}

(Soon Oh)
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

(Lillie Golson)
Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOON M OH
05/11/2012

LILLIE D GOLSON
05/11/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065156s010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RANBAXY

RANBAXY INC. 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

December 22, 2010

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

FDA-GATEWAY
LABELING SUPPLEMENT - CBE

Reference: **ANDA 065156**
Minocycline Hydrochloride Tablets 50 mg, 75 mg & 100 mg
Reference Listed Drug Update

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited Approved ANDA 065156 Minocycline Hydrochloride Tablets 50 mg, 75 mg & 100 mg. Reference is also made to the recently approved labeling for Reference Listed Drug MINOCIN® (NDA 050649/S-023 approved on 09/14/2010).

Based on the above Ranbaxy Laboratories Limited has revised its labeling as follows:

Package Insert: ***DESCRIPTION; WARNINGS; ADVERSE REACTIONS, Other; DOSAGE AND ADMINISTRATION; HOW SUPPLIED SECTION*** *and* ***PATIENT INFORMATION LEAFLET****.*

Container Label: ***PDP****;* ***Usual Dosage*** *information*

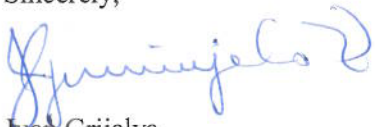
Ranbaxy is hereby submitting the revised package insert and container labels through this e-labeling submission. In addition Ranbaxy has also revised its **Structured Product Labeling** in XML format. For ease of reference an annotated side-by-side comparison of revised vs. previously submitted package insert and container labels has been included with this e-labeling submission.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the labeling for this submission has been submitted through the FDA-ESG and is approximately 7 MB in size. The contents of the submission have been scanned for viruses using McAfee Virus Scan Enterprise 8.0.0 updated on December 22, 2010

Please also note, the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8058 or Mr. Scott D. Tomsky at 609-720-5609 if you have any questions regarding this submission.

Sincerely,



Juan Grijalva
Senior Regulatory Affairs Associate (*for*)
Scott D. Tomsky
Official Agent for Ranbaxy Laboratories Inc.
JuanG@ranbaxy.com

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 21, 2011

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

FDA-ESG
AMENDMENT TO CBE
LABELING SUPPLEMENT

Reference: **ANDA 065156**
Minocycline Hydrochloride Tablets 50 mg, 75 mg & 100 mg
Amendment to the CBE Labeling Supplement submitted December 22, 2010

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited Approved ANDA 065156 Minocycline Hydrochloride Tablets 50 mg, 75 mg & 100 mg. Reference is also made to the Changes Being Effected Labeling Supplement submitted on December 22, 2010.

Through this submission, Ranbaxy Laboratories Limited is hereby amending the Changes Being Effected (CBE) Labeling supplement submitted on December 22, 2010 for Minocycline HCl Tablets, USP – 50 mg, 75 mg, 100 mg to correct the HOW SUPPLIED section.

In the December 22, 2010 CBE Labeling Supplement, the **Final Printed Labeling** (final-pi) and the **data elements** section of the Structured Product Labeling (SPL) inadvertently listed the pill imprint as R189 (**50 mg**), R190 (**75 mg**) & R191 (**100 mg**) instead of RI89, RI90 & RI91 respectively. Please note, all other documents related to the package insert (compare-pi, final-pi-text) listed the correct pill imprint and therefore are not being submitted.

The correct version of the **Final Printed Labeling** and **SPL** are being provided with this submission.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the labeling for this submission has been submitted through the FDA-ESG and is approximately 2 MB in size. The contents of the submission have been scanned for viruses using McAfee Virus Scan Enterprise 8.5 updated on June 21, 2011. Please also note, the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8057 (email: manisha.sharma@ranbaxy.com) or Mr. Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Manisha Sharma
Senior Regulatory Affairs Associate (*for*)
Scott D. Tomsky
Official Agent for Ranbaxy Laboratories Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20855

ANDA 065156/S-010 **COMPLETE RESPONSE**

Ranbaxy Laboratories Limited
Attn: Scott D. Tomsky
600 College Road East
Princeton, NJ 08540

Dear Sir:

This is in reference to your supplemental new drug application dated December 22, 2010 and June 21, 2011 submitted pursuant to 21 CFR 314.70(c) (6) [Supplement – Changes Being Effected] regarding your abbreviated new drug application for Minocycline Hydrochloride Tablets USP, 50 mg, 75 mg, and 100 mg.

This supplemental new drug application provides for revisions to the package insert labeling in accordance with the labeling of the innovator drug, Minocin® Pellet-Filled Capsules (NDA 50649/S-023), approved September 14, 2010 and minor revisions to the container label. The supplemental application dated June 21, 2011 is to amend the CBE Labeling supplement submitted on December 22, 2010 to correct the imprinting of the tablets in the HOW SUPPLIED section of the FPL and the data elements section of the SPL.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. GENERAL

We note that you revised the [redacted] (b) (4) from the one approved by the Agency (S-008 approved October 27, 2008). We are not able to approve the labeling until the revised [redacted] (b) (4) are found acceptable. Please submit the CMC information associated with these changes and/or comment.

2. CONTAINER: 100s and 500s for 50 mg and 75 mg, and 50s and 500s for 100 mg

Please revise storage recommendations to read "Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. [Note; "20°" rather than "20" and "68°" rather than "68"]

3. PROFESSIONAL INSERT:

a. CLINICAL PHARMACOLOGY

Please note that the RLD, ANDA 65131, by Medicis Pharmaceutical Corporation has CLINICAL PHARMACOLOGY section specific for the tablet dosage form. Revise accordingly. Please contact Soon Oh (Soon.Oh@fda.hhs.gov) for the RLD labeling.

"CLINICAL PHARMACOLOGY

Following a single dose of one 100 mg tablet of minocycline hydrochloride administered to 28 normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 3 hours (average 1.71 hours) and ranged from 491.71 to 1292.70 ng/mL (average 758.29 ng/mL). The serum half-life in the normal volunteers ranged from 11.38 to 24.31 hours (average 17.03 hours).

When minocycline hydrochloride tablets were given concomitantly with a meal, which included dairy products, the extent of absorption of minocycline hydrochloride tablets was slightly decreased (6%). The peak plasma concentrations were slightly decreased (12%) and delayed by 1.09 hours when administered with food, compared to dosing under fasting conditions.

In previous studies with other minocycline dosage forms, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers was one-half to one-third that of other tetracyclines."

b. HOW SUPPLIED

i. See comments under GENERAL

ii. See comment under CONTAINER

iii. We note that the [redacted] (b) (4) for 100 mg tablet is not consistent with the one in the previous package insert. Please clarify and/or comment.

iv. Revise to read "Dispense in a tight, light resistant container as defined in the USP." or "Dispense in tight, light resistant containers as defined in the USP."

c. REFERENCES

i. Ref 1, 4th line – Revise to read "…, Suite 1400, Wayne, PA, January 1997." [Note; comma included after "Wayne"]

ii. Ref 2, 4th line – Revise to read "…1400, Wayne, PA…" [Note; comma included after "1400"]

iii. Ref 4, 3rd and 4th line – Revise to read "…940 West Valley Road, Suite 1400, Wayne, PA…" [Note; comma included after "Road", "1400", and "Wayne"]

4. SPL - DATA ELEMENTS

Active Ingredient/Active Moiety – Basis of Strength

Please note that the strength of your drug product is based on "minocycline" rather than "minocycline hydrochloride". Revise accordingly.

5. PATIENT INFORMATION LEAFLET

Satisfactory in FPL as of the December 22, 2010 submission.

Please submit your response as an amendment to this supplemental application and state on the top right of the cover letter "Amendment to Complete Response Action S-010". To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

In addition to final printed labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved.

If you have any questions, please contact Soon Oh, labeling reviewer, at (240) 276-8996 or by e-mail at soon.oh@fda.hhs.gov.

Sincerely yours,

{*see appended electronic signature page*}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LILLIE D GOLSON
07/13/2011
for Wm. Peter Rickman

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 5, 2011

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

FDA ESG

AMENDMENT TO COMPLETE RESPONSE ACTION S-010

Reference: **ANDA 065156**
Minocycline Hydrochloride Tablets 50 mg, 75 mg and 100 mg
Amendment to Complete Response Action S-10

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited Approved ANDA 065156 for Minocycline Hydrochloride Tablets 50 mg, 75 mg and 100 mg. Reference is also made to the following:

- The CBE supplement dated December 22, 2010 was submitted to include revisions to package insert as per the most current approved labeling of Reference listed drug **MINOCIN®** (NDA 050649/S-023) dated 09/14/2010.
- The supplemental application dated June 14, 2011 was submitted to amend the CBE supplement dated December 22, 2010 to correct the imprint of tablets under the HOW SUPPLIED section of the **FPL** and data elements section of the **SPL.**
- FDA correspondence letter received from the Agency dated July 13, 2011.

Based on the above, Ranbaxy is hereby submitting its revised **Package Insert, Patient Information Leaflet, Container Labels** and **Structured Product Labeling** (in XML format). For ease of reference an **annotated side-by-side comparison** of revised vs. previously submitted Package Insert and **annotated Container Labels** have been included with this e-labeling submission. For complete details please see the **complete-response.pdf**

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the labeling for this submission has been submitted through the FDA-ESG and is approximately 4 MB in size. The contents of the submission have been scanned for viruses using McAfee Virus Scan Enterprise 8.5 updated on October 5, 2011. Please also note, the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8057 (email: manisha.sharma@ranbaxy.com) or Mr. Scott D. Tomsky at 609-720-5609 (email:scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Manisha Sharma
Senior Regulatory Associate (*for*)
Scott D. Tomsky
Official Agent for Ranbaxy Laboratories Limited