

 \mathbf{R} only

DESCRIPTION:
Pyrazinamide, the pyrazine
analogue of nicotinamide, is an
antituberculous agent. It is a
white crystalline powder, stable at room temperature, and
sparingly soluble in water.
Pyrazinamide has the following
structural formula:



M.W. 123.1'
Each pyrazinamide tablet for oral administration contain 500 mg of pyrazinamide an the following inactive ingredi ents: colloidal silicon dioxide croscarmellose sodium, diba sic calcium phosphate (dihy drate), microcrystalline cellu lose, and stearic acid.

Site Galumi pricopystalline cellulose, and stearic acid.

CLINICAL PHARMAGOLOGY:

Pyrazinamide is well absorbed from the GI tract and attains peak plasma concentrations great plasma concentrations generally range from 30 to 50 mcg/mL with doses of 20 to 25 mg/kg. It is widely distributed in body tissues and fluids including the liver, lungs and cerebrospinal fluid (CSP). The CSF concentration is approximately equal to concurrent steady-state plasma concentrations with inflamed mening-es. 1 Pyrazinamide is approximately 10% bound to plasma proteins. ² The Half-life (t 12) of pyrazinamide is 9 to 10 hours in patients with inmanarenal and hepatic function. Pyrazinamide is hydrovjed in patients with impaired renal or hepatic function. Pyrazinamide is hydrovjed in the liver to its raincipal caid. Pyrazinoic acid is hydroxylated to the main excretory product, 5-hydroxypyrazinoic acid. ³

acid.³
Approximately 70% of an ora dose is excreted in the urine mainly by glomerular filtration within 24 hours.³

within 24 hours.³
Pyrazinamide may be bacteriostatic or bactericidal against
Mycobacterium tuberculosis
depending on the concentration of the drug attained at the
site of infection. The mechanism of action is unknown. In
vitro and in vivo the drug is
active only at a slightly acidic
pH.

ptl.

INDICATIONS AND USAGE:
Pyrazinamide is indicated for
the initial treatment of active
tuberculosis in adults and children when combined with
other antituberculous agents.
(The current recommendation
of the CDC for drug-susceptible disease is to use a sixmonth regimen for initial treatment of active tuberculosis,
consisting of soniazid, rifampin and pyrazinamide given
for 2 months, followed by isoniazid and rifampin for 4
months. *4)

(Patients with drug-register.

Patients with drug-resistant disease should be treated with egimens individualized to their situation. Pyrazinamide frequently will be an important component of such therapy.) atients

(In patients with concomitant HIV infection, the physician should be aware of current rec-ommendation of CDC. It is possible these patients may require a longer course of treatment.) It is also indicated after treat-ment failure with other primary drugs in any form of active tuberculosis.

azinamide should only t d in conjunction with oth ctive antituberculous agent

effective antituberculous agents.

"See recommendations of Center for Disease Control (CDC)
and American Thoracic Society
for complete regimen and
dosage recommendations.4

CONTRAINDICATIONS:

Pyrazinamide is contraindicated in persons:
-with severe hepatic damage.
-who have shown hypersensitivity to it.
-with acute gout.

WARNINGS: -with acute gout.

WARNINGS:

Patients started on pyrazinamide should have baseline
serum uric acid and liver function determinations. Those
patients with preexisting liver
disease or those at increased
risk for drug related hepatitis
(e.g., alcohol abusers) should
be followed closely.

Persinomide should he die.

be followed closely.

Pyrazinamide should be discontinued and not be resumed
if signs of hepatocellular damage or hyperuricemia accompanied by an acute gouty
arthritis appear.

arthritis appear.

PRECAUTIONS:
General:

Pyrazinamide inhibits renal
excretion of urates, frequently
resulting in hyperuricemia
which is usually asymptomatic. If hyperuricemia is
accompanied by acute gouty
arthritis, pyrazinamide should
be discontinued. Pyrazinamide should be used with caution in patients with a history of diabetes mellitus, as management may be more dif-ficult.

ficult.

Primary resistance of M. tuberculosis to pyrazinamide is uncommon. In cases with known or suspected drug resistance, in vitro susceptibility tests with recent cultures of M. tuberculosis against pyrazinamide and the usual primary drugs should be performed. There are few reliable in vitro tests for pyrazinamide resistance. A reference laboratory capable of performing these studies must be employed. Information for Patients:

studies must be employed. Information for Patients: Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yel-lowish discoloration of the skin and eyes, pain or swelling of the joints. the joints.

Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.

must be stressed.

Laboratory Tests:
Baseline liver function studies [especially ALT (SGPT), AST (SGOT) determinations] and uric acid levels should be determined prior to therapy. Appropriate laboratory testing should be performed at periodic intervals and if any clinical signs of symptoms occur during therapy.

Putual Aboratory Test

Drug/Laboratory Test
Interactions:
Pyrazinamide has been reported to interfere with ACETEST®
and KETOSTIX® urine tests to
produce a pink-brown color.⁵

produce a pink-brown color.*

Carcinogenicity, Mutagenicity, Impairment of Fertilitys.73.

In lifetime bioassays in rats and mice, pyrazinamide was administered in the diet at concentrations of up to 10,000 ppm. This resulted in estimated daily doses for the mouse of 2 g/kg, or 40 times the maximum human dose, and for the rat of 0.5 g/kg, or 10 times the maximum human dose. Pyrazinamide was not carcinogenic in rats or male mice and no conclusion was possible for female mice due to insufficient numbers of surviving control mice.

Pyrazinamide was not muta-

Pyrazinamide was not muta-genic in the Ames bacterial test, but induced chromosomal aberrations in human lympho-cyte cell cultures.

aperations in numery improcyte cell cultures.

Pregnancy: Teratogenic

Effects-Pregnancy Category C

Animal reproduction studies
have not been conducted with
pyrazinamide. It is also not
known whether pyrazinamide
can cause fella harm when
administered to a pregnant
woman or can affect reproduction capacity. Pyrazinamide
should be given to a pregnant
woman only if clearly needed.

Nursing Mothers:

Pyrazinamide has been found
in small amounts in breast
milk. Therefore, it is advised
that pyrazinamide be used with
caution in nursing mothers
taking into account the riskbenefit of this therapy.⁹

Pediatric Use:

taking into account use imbenefit of this therapy.⁹

Pediatric Use:
Pyrazinamide regimens employed in adults are probably equally effective in pediatric patients.⁴4:191. Pyrazinamide appears to be well tolerated in pediatric patients.

Periatric Use:¹²

Clinical studies of pyrazinamide did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other report-ed clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cau-



tious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic or renal function, and of concomitant disease or other drug therapy. It does not appear that patients with impaired renal function require a reduction in dose. It may be prudent to select doses at the low end of the dosing range, however.¹³

ADVERSE REACTIONS: General: Fever, porphyria and dysuria have rarely been reported. Gout (see PRECAUTIONS).

Gout (see PRECAUTIONS).

Gastrointestinal:
The principal adverse effect is
a hepatic reaction (see WARNINGS). Hepatotoxicity appears
to be dose related, and may
appear at any time during therapy. Gl disturbances including
nausea, vomiting and anorexia
have also been reported.

Hematologic and Lymphatic:
Thrombocytopenia and sideroblastic anemia with erythroid
hyperplasia, vacuolation of
erythrocytes and increased
serum iron concentration have
occurred rarely with this drug.
Adverse effects on blood colcting mechanisms have also
been rarely reported.

Other:

been rarety top.

Other:
Mild arthralgia and myalgia have been reported frequently hypersensitivity reactions including rashes, urticaria, and pruritis have been reported. Fever, acne, photosensitivity, porphyria, dysuria and interstitial nephritis have been reported rarely.

ed rarely.

OVERDOSAGE:

Overdosage experience is limled. In one case report of overdose, abnormal liver function
tests developed. These spontaneously reverted to normal
when the drug was stopped.
Clinical monitoring and supportive therapy should be
employed, Pyrazinamide is dialyzable. 13 lyzable. 13

DOSAGE AND

ADMINISTRATION:
Pyrazinamide should always be administered with other effective antituberculous drugs. It is administered for the initial 2 months of a 6-month or longer treatment regimen for drug-susceptible patients. Patients who are known or suspected to have drug-resistant disease should be treated with regimens individualized to their situation.

Pyrazinamide fr an important such therapy. Such therapy.

Patients with concomitant HIV infection may require longer courses of therapy. Physicians treating such patients should be alert to any revised recommendations from CDC for this group of patients.

group of patients.

Usual dose: Pyrazinamide is administered orally, 15 to 30 mg/kg once daily. Older regimens employed 3 or 4 divided doses daily, but most current recommendations are for once a day. Three grams per day should not be exceeded. The CDC recommendations do not exceed 2 g per day when given as a daily regimen (see table).

Alternatively a twice weekly

as a daily regimen (see table).

Alternatively, a twice weekly dosing regimen (50 to 75 mg/kg twice weekly based on lean body weight) has been developed to promote patient compliance with a regimen on an outpatient basis. In studies evaluating the twice weekly regimen, doses of pyrazinamide in excess of 3 g twice weekly have been administered. This exceeds the recommended maximum 3 g/daily dose. However, an increased incidence of adverse reactions has not been reported.

This table is taken from the

has not been reported.
This table is taken from the
CDC-American Thoracic Society joint recommendations.⁴

Recommended Drugs for the
Initial Treatment of
Tuberculosis in Children
and Adults

Daily Dose*

Drug Children Adults

Adults

Drug Adults

Adult

15 to 2 mg/kg PO i to ng/k PO

in Ch Drug Isoniazid Rifampin Pyrazinami Streptomyc Ethambutol 1 g** 2.5 g

Twice Weekly Dose
Children Adults
15 ng/kg
Max. 900 mg
Max. 900 mg
Max. 900 mg
Max. 900 mg
Max. 600 mg

Ethambutol 50 mg/lg 50 mg/lg

Definition of abbreviations: P0-perorally, M - Intransoularly,

"Doses based on weight should be
adjusted as weight changes.

"In persons older then 60 yr of age
the daily dose of firstpornyion should
be limited to 10 mg/lg with a maximal
dose of 750 mg.

HOW SUPPLIED:

Pyrazinamide Tablets USP contain pyrazinamide 500 mg.
They are supplied as white,
round, scored tablets debossed "VP/012" in containers of
60 tablets NDC# 61748-012-06, in containers of
500 tablets NDC# 61748-012-05,

Son and in hospital unit-dose
cartons of 100 tablets (in strips
of 10 tablets NDC# 61748-012-05,

50, and in hospital unit-dose
cartons of 100 tablets (in strips
of 10 tablets per strip) NDC#
of 1748-012-05,

Total tablets per strip) NDC#
of 1748-012-05.

Storage: Store in a well-closed container at controlled room temperature, 15°C to 30°C (59°F to 86°F).

Dispense in a well-closed container with a child-resistant closure.

Marketed by: VersaPharm Incorporate Marietta, GA 30062

Manufactured by: MIKART, INC. Atlanta, GA 30318 04/01 590B00

code 590800

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