

Physicians' Desk Reference®

PDR
33
EDITION
1979

Publisher • CHARLES E. BAKER, Jr.

Director of Production
JEROME M. LEVINE

Managing Editor
BARBARA B. HUFF

Medical Consultant
IRVING M. LEVITAS, M.D.

Manager of Production Services
ELIZABETH H. CARUSO

Index Editor
GYNNEED L. KELLY

Editorial Assistants
F. EDYTHE PATERNITI
EMILY B. BROGELER

Business Manager
EDWARD R. BARNHART

Administrative Assistant
DIANE M. WARD

Director of Printing
RALPH G. PELUSO

Circulation Director
MARC ROSS

Fulfillment Manager
JACQUELINE STAHLIN

Research Director
STEPHEN J. SORKENN



Copyright © 1979 by Litton Industries, Inc. Published by Medical Economics Company, a Litton division, at Oradell, N.J. 07649. All rights reserved. None of the content of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the prior written permission of the publisher.
ISBN 0-87489-999-0

Merck Sharp & Dohme—Cont.

Dosage and Administration

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND THE RESPONSE OF THE PATIENT.

Each PERIACTIN tablet contains 4 mg of cyproheptadine hydrochloride. Each 5 ml of PERIACTIN syrup contains 2 mg of cyproheptadine hydrochloride.

Although intended primarily for administration to children, the syrup is also useful for administration to adults who cannot swallow tablets.

Children

The total daily dosage for children may be calculated on the basis of body weight or body area using approximately 0.25 mg/kg/day (0.11 mg/lb/day) or 8 mg per square meter of body surface (8 mg/M²). In small children for whom the calculation of dosage based upon body size is most important, it may be necessary to use PERIACTIN syrup to permit accurate dosage.

Age 2 to 6 years

The usual dose is 2 mg (½ tablet or 1 teaspoon) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 12 mg a day.

Age 7 to 14 years

The usual dose is 4 mg (1 tablet or 2 teaspoons) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 16 mg a day.

Adults

The total daily dose for adults should not exceed 0.5 mg/kg/day (0.23 mg/lb/day). The therapeutic range is 4 to 20 mg a day, with the majority of patients requiring 12 to 16 mg a day. An occasional patient may require as much as 32 mg a day for adequate relief. It is suggested that dosage be initiated with 4 mg (1 tablet or 2 teaspoons) three times a day and adjusted according to the size and response of the patient.

How Supplied

No. 3276—Tablets PERIACTIN, containing 4 mg of cyproheptadine hydrochloride each, are white, round, scored compressed tablets, coded MSD 62. They are supplied as follows: NDC 0006-0062-68 bottles of 100. (6505-00-890-1884 4 mg 100's)

[Shown in Product Identification Section]

No. 3289X—Syrup PERIACTIN, 2 mg per 5 ml is a clear, yellow, syrupy liquid. Contains alcohol 5%, with sorbic acid 0.1% added as preservative and is supplied as follows: NDC 0006-3289-74 bottles of 473 ml.

A.H.F.S. 4:00

DC 6589610 Issued August 1978

PNEUMOVAX®
(pneumococcal vaccine, polyvalent, MSD)

Description

PNEUMOVAX (Pneumococcal Vaccine, Polyvalent, MSD), is derived from the capsules of cultured pneumococci. This vaccine is indicated for immunization against infections caused by pneumococci. The vaccine affords protection against the 14 most prevalent or invasive capsular types accounting for at least 80% of pneumococcal disease isolates as deter-

mined by on-going surveillance. Protective capsular type-specific antibody levels develop by the third week following vaccination.

PNEUMOVAX consists of polysaccharides isolated from the capsules of bacteria of the individual types and is manufactured according to methods developed by the MERCK SHARP & DOHME Research Laboratories. The vaccine is formulated so that each 0.5 ml dose contains 50 µg of each polysaccharide type dissolved in isotonic saline solution containing phenol 0.25% added as preservative.

14 Pneumococcal Capsular Types Included in PNEUMOVAX

Nomenclature	Pneumococcal Types													
U.S.	1	2	3	4	6	8	9	12	14	19	23	25	51	56
Danish	1	2	3	4	6A	8	9N	12F	14	19F	23F	25	7F	18C

Actions

Pneumococcal infection is a leading cause of death throughout the world and a major cause of pneumonia, meningitis, and otitis media. The exact incidence of pneumococcal infection is not known. On the basis of the limited epidemiological data obtained from studies in municipal hospitals where the incidence might be higher than that found in the average population, it is estimated that there are annually 200,000 to 1,000,000 cases of pneumococcal pneumonia in the United States, and between 13,200 and 68,000 deaths resulting therefrom. Thus, the attack rate for pneumococcal pneumonia is estimated to be between 1 and 5 cases per 1,000 persons per year, and death is estimated to occur in about 1 of 15 cases. Based on these same data, about 25% of all persons with pneumococcal pneumonia develop bacteremia. Death occurs in about 28% of these bacteremic patients more than 50 years of age.

In the United States, pneumococcal meningitis occurs principally in young children, with annual rates of about 3 to 11 per 100,000 children less than 5 years old. Within the first two years of life, about 15 to 20% of all children develop otitis media caused by pneumococci, and 50% of all children develop such illness within the first 10 years of life (see under INDICATIONS). Invasive pneumococcal disease causes high morbidity and mortality in spite of effective antimicrobial control by antibiotics. These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness, and irrespective of antimicrobial therapy. Older persons, individuals with chronic debilitating diseases, and persons with absent or impaired splenic function, including those with homozygous sickle cell anemia and sickle thalassemia, are especially susceptible to severe pneumococcal disease.

Presently, there are 83 known pneumococcal capsular types. However, the preponderance of pneumococcal disease is caused by only some capsular types. For example, a 10-year (1952-1962) surveillance at a New York medical center showed that 56% of all deaths due to pneumococcal pneumonia were caused by 6 capsular types and that approximately 78% of all pneumococcal pneumonias were caused by 12 capsular types. Such unequal distribution of pneumococcal capsular types causing disease has been shown throughout the world. It is on

the basis of this information that the pneumococcal vaccine is composed of 14 capsular types. It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease. PNEUMOVAX consists of 14 different capsular polysaccharides which represent at least 80% of pneumococcal disease isolates in the U.S.A. and Europe. Studies in humans have demonstrated the immunogenicity (antibody-stimulating capability) of each of the 14 capsular types when tested in polyvalent vaccines. Adults of all ages and children of 2 years of age or older responded immunologically to the vaccines. In a recent study of PNEUMOVAX, at least 90% of all adults showed a fourfold or greater increase in type-specific antibody for each vaccine capsular type.

The protective efficacy of pneumococcal vaccines containing 6 and 12 capsular polysaccharides was investigated in controlled studies of gold miners in South Africa, in whom there is a high attack rate for pneumococcal pneumonia. Capsular type-specific attack rates for pneumococcal pneumonia were observed for the period from 2 weeks through about 1 year after vaccination. The rates for pneumonia caused by the same capsular types represented in the vaccines are given below. Protective efficacy was 76% and 92%, respectively, in the two studies for the capsular types represented. [See table below].

In similar studies carried out by Dr. R. Austrian and associates using similar pneumococcal vaccines, prepared for the National Institute of Allergy and Infectious Diseases by a different source, the reduction in pneumonias caused by the vaccine capsular types was 79%. Type-specific reduction in pneumococcal bacteremia was 82%. A preliminary report suggests efficacy of the vaccine in persons over two years of age in preventing severe pneumococcal disease and bacteremia in patients with sickle cell anemia and in individuals without spleens or those who have impaired splenic function. The duration of protective effect of PNEUMOVAX is presently unknown, but it has been shown in previous studies with other pneumococcal vaccines that antibody induced by the vaccine may persist for as long as 5 years. Type-specific antibody levels induced by PNEUMOVAX have been observed to decline over a 20-month period of observation, but remain significantly above preimmunization levels in almost all recipients who manifest an initial response.

Because of the decline in antibody levels, revaccination may be considered. Available data suggest that revaccination should not be carried out at less than 3-year intervals so as to minimize the frequency and severity of local reactions, especially in persons who have retained high antibody levels. Long-term surveillance of antibody levels in immunized individuals is continuing.

Indications

PNEUMOVAX is indicated for immunization against lobar pneumonia and bacteremia, caused by those types of pneumococci included in the vaccine, in all persons two years of age or older in whom there is an increased risk of morbidity and mortality from pneumococcal pneumonia. These include: (1) persons having chronic physical conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders; (2) persons in chronic care facilities; (3) persons convalescing from severe disease; (4) persons 50 years of age or older. Preliminary data suggest the vaccine is efficacious for preventing severe pneumonic disease and bacteremia in persons over two years of age with sickle cell anemia and in individuals who have had a splenectomy or who have im-

paired splenic functions over two years of age. It is expected that effective immunization with PNEUMOVAX will prevent infection of the meninges or fracture of the cerebrosplenic fluid barrier, the effect of which is to prevent pneumonia.

Contraindications

Contraindications to the vaccine are hypersensitivity to any of the antigens, immediate or delayed allergic reactions to any of the components, or a history of severe allergic reactions to any of the components. Do not give to females; the possible fetal development of children less than 2 years of age is not known. PNEUMOVAX is not recommended for use in this age group.

Warnings

PNEUMOVAX is a vaccine. It is not intended for use in persons with immunosuppressive conditions. Intradermal and local reactions may occur.

Precautions

Any febrile response to the vaccine is usually mild and self-limiting. If the vaccine is given to persons with severe local reactions, especially in persons who have retained high antibody levels, a severe local reaction may occur. Patients who have had severe local reactions to previous pneumococcal vaccines should not receive PNEUMOVAX. Caution and appropriate medical attention should be given to patients with severe local reactions to previous pneumococcal vaccines. Available data suggest that revaccination should not be carried out at less than 3-year intervals so as to minimize the frequency and severity of local reactions, especially in persons who have retained high antibody levels. Long-term surveillance of antibody levels in immunized individuals is continuing.

Adverse Reactions

Local reactions, such as erythema, tenderness, and swelling, usually occur commonly. In a study of 14 capsular types, 92% showed reactions principally by local reactions at the injection site. Low grade fever is usually mild and self-limiting. Reactions of greater severity are unusual. Reactions have been reported.

Number of Capsular Types in Pneumococcal Vaccine	Rate/1000 for Pneumonia Caused by Homologous Capsular Types		Protective Efficacy
	Vaccinated Group	Control Group	
6	9.2	38.3	76%
12	1.4	16.7	92%

ion that the pneumo-
d of 14 capsular types.
at the purified pneumo-
saccharides induce
that such antibody is
neumococcal disease.
f 14 different capsu-
h represent at least
sease isolates in the
lies in humans have
nogenicity (antibody-
each of the 14 capsu-
polyvalent vaccines.
dren of 2 years of age
ologically to the vac-
f PNEUMOVAX, at
howed a fourfold or
specific antibody for
se.

f pneumococcal vac-
capsular polysaccha-
controlled studies of
a, in whom there is a
ococcal pneumonia.
ack rates for pneu-
observed for the
h about 1 year after
neumonia caused
s represented in the
Protective efficacy
ctively, in the two
pes represented.

out by Dr. R. Aus-
similar pneumococ-
the National Insti-
tious Diseases by a
tion in pneumonias
ilar types was 79%.
pneumococcal vac-
inary report sug-
in persons over two
severe pneumococ-
a in patients with
ividuals without
impaired splenic

ffect of PNEUMO-
1, but it has been
ith other pneumo-
dy induced by the
long as 5 years.
vels induced by
served to decline
eervation, but re-
vaccination levels
manifest an initial

ntibody levels, re-
d. Available data
ould not be car-
intervals so as to
severity of local
ons who have re-
ong-term surveil-
immunized individ-

for immunization
and bacteremia,
mococci included
wo years of age or
increased risk of
m pneumococcal
) persons having
uch as chronic
chronic broncho-
enal failure, and
ronic metabolic
ic care facilities;
a severe disease;
older.
vaccine is effica-
eumonic disease
ver two years of
id in individuals
or who have im-

paired splenic function, and in pediatric pa-
tients over two years of age with nephrotic syn-
drome. It is expected also that the vaccine will
be found effective in preventing pneumococcal
meningitis of bacteremic origin. However,
PNEUMOVAX may not be effective in prevent-
ing infection resulting from basilar skull
fracture or from external communication with
cerebrospinal fluid. Studies are under way to
determine the effectiveness of the vaccine for
preventing pneumococcal otitis media in in-
fants.

Contraindications

Hypersensitivity to any component of the vac-
cine. Epinephrine injection (1:1000) must be
immediately available should an acute ana-
phylactoid reaction occur due to any compo-
nent of the vaccine.

Do not give PNEUMOVAX to pregnant
females; the possible effects of the vaccine on
fetal development are unknown.

Children less than 2 years of age do not re-
spond satisfactorily to the capsular types of
PNEUMOVAX that are most often the cause
of pneumococcal disease in this age group. Ac-
cordingly, PNEUMOVAX is not recommended in
this age group.

Warnings

PNEUMOVAX will not immunize against cap-
sular types of pneumococcus other than those
contained in the vaccine (see above).

If the vaccine is used in persons receiving im-
munosuppressive therapy, the expected serum
antibody response may not be obtained.
Intradermal administration may cause severe
local reactions.

Precautions

Any febrile respiratory illness or other active
infection is reason for delaying use of
PNEUMOVAX, except when, in the opinion of
the physician, withholding the agent entails
even greater risk.

Caution and appropriate care should be exer-
cised in administering PNEUMOVAX to in-
dividuals with severely compromised cardiac
and/or pulmonary function in whom a sys-
temic reaction would pose a significant risk.
Patients who have had episodes of pneumococ-
cal pneumonia or other pneumococcal infec-
tion in the preceding three years may have
high levels of pre-existing pneumococcal an-
tibodies which may result in increased reac-
tions to PNEUMOVAX, mostly local but occa-
sionally systemic. Caution should be exercised
if such patients are considered for vaccination
with PNEUMOVAX.

Available data suggest that revaccination be-
fore 3 years may result in more frequent and
severe local reactions at the site of injection,
especially in persons who have retained high
antibody levels (see DOSAGE AND ADMINIS-
TRATION).

Children under 2 years of age may not obtain a
satisfactory antibody response to some pneu-
mococcal capsular types. Therefore, the vac-
cine should not be used in this age group.

Adverse Reactions

Local erythema and soreness at the injection
site, usually of less than 48 hours duration,
occurs commonly; local induration occurs less
commonly. In a study of PNEUMOVAX (con-
taining 14 capsular types) in 26 adults, 24
(92%) showed local reaction characterized
principally by local soreness and/or induration
at the injection site within 2 days after vac-
cination.

Low grade fever (less than 100.9°F) occurs occa-
sionally and is usually confined to the 24-hour
period following vaccination.

Although rare, fever over 102°F has been re-
ported.

Reactions of greater severity, duration, or ext-
ent are unusual. Rarely, anaphylactoid reac-
tions have been reported.

Dosage and Administration

Do not inject intravenously.

Administer a single 0.5 ml dose of PNEUMO-
VAX subcutaneously or intramuscularly (prefer-
ably in the deltoid muscle or lateral mid-
thigh), with appropriate precautions to avoid
intravascular administration. (See INDICA-
TIONS.) Intradermal administration should be
avoided.

Until further information on duration of im-
munity becomes available, revaccination
should not be considered at less than 3 year
intervals, since protective antibody levels are
believed to persist for substantial periods in
most vaccinated persons. Available data sug-
gest that revaccination before 3 years may re-
sult in more frequent and severe local reac-
tions at the site of injection, especially in per-
sons who have retained high antibody levels
(see ACTIONS).

Storage and Use

Store unopened and opened vials at 2-8°C
(35.6-46.4°F). The vaccine is used directly as
supplied. No dilution or reconstitution is ne-
cessary. Phenol 0.25% added as preservative.

It is important to use a separate sterile syringe
and needle for each individual patient to pre-
vent transmission of hepatitis B and other in-
fectious agents from one person to another. All
vaccine must be discarded by the expiration
date.

Single-Dose and 5-Dose Vials

For Syringe Use Only: Withdraw 0.5 ml
from the vial using a sterile needle and sy-
ringe free of preservatives, antiseptics and
detergents.

How Supplied

No. 4666—PNEUMOVAX contains one 5-dose
vial of liquid vaccine, NDC 0006-4666-00. For
use with syringe only.

No. 4689—PNEUMOVAX is supplied as fol-
lows: NDC 0006-4689-00. A box of 5 individ-
ual cartons, each containing a single dose vial
of vaccine.

A.H.F.S. 80:12

DC7014802 Issued June 1978
© MERCK & CO., INC., 1977. All rights re-
served.

SINEMET® Tablets

B

Description

SINEMET is a combination of carbidopa and
levodopa. Before instituting therapy with
SINEMET, physicians should be familiar with
directions for its use.

When SINEMET is to be given to patients
who are being treated with levodopa,
levodopa must be discontinued at least
eight hours before therapy with SINEMET
is started. In order to reduce adverse reac-
tions, it is necessary to individualize ther-
apy. See the WARNINGS and DOSAGE
AND ADMINISTRATION sections before
initiating therapy.

Carbidopa, an inhibitor of aromatic amino acid
decarboxylation, is a white, crystalline com-
pound, slightly soluble in water, with a molecu-
lar weight of 244.3. It is designated chemically
as (—)-L- α -hydrazino- α -methyl- β -(3,4-dihy-
droxybenzene) propanoic acid monohydrate.
Tablet content is expressed in terms of anhy-
drous carbidopa which has a molecular weight
of 226.3.

Levodopa, an aromatic amino acid, is a white,
crystalline compound, slightly soluble in wa-
ter, with a molecular weight of 197.2. It is de-
signed chemically as (—)-L- α -amino- β -
(3,4-dihydroxybenzene) propanoic acid.

SINEMET, a combination of carbidopa and
levodopa, is supplied as tablets in two
strengths:

SINEMET-10/100, containing 10 mg of car-
bidopa and 100 mg of levodopa
SINEMET-25/250, containing 25 mg of car-
bidopa and 250 mg of levodopa

Actions

Current evidence indicates that symptoms of
Parkinson's disease are related to depletion of
dopamine in the corpus striatum. Administra-
tion of dopamine is ineffective in the treatment
of Parkinson's disease apparently because it
does not cross the blood-brain barrier. How-
ever, levodopa, the metabolic precursor of do-
pamine, does cross the blood-brain barrier, and
presumably is converted to dopamine in the
basal ganglia. This is thought to be the mech-
anism whereby levodopa relieves symptoms of
Parkinson's disease.

When levodopa is administered orally it is rap-
idly converted to dopamine in extracerebral
tissues so that only a small portion of a given
dose is transported unchanged to the central
nervous system. For this reason, large doses of
levodopa are required for adequate therapeutic
effect and these may often be attended by nau-
sea and other adverse reactions, some of which
are attributable to dopamine formed in extra-
cerebral tissues.

Carbidopa inhibits decarboxylation of periph-
eral levodopa. It does not cross the blood-brain
barrier and does not affect the metabolism of
levodopa within the central nervous system.

Since its decarboxylase inhibiting activity is
limited to extracerebral tissues, administra-
tion of carbidopa with levodopa makes more
levodopa available for transport to the brain.
In dogs, reduced formation of dopamine in ex-
tracerebral tissues, such as the heart, provides
protection against the development of dopa-
mine-induced cardiac arrhythmias. Clinical
studies tend to support the hypothesis of a sim-
ilar protective effect in humans although con-
trolled data are too limited at the present time
to draw firm conclusions.

Carbidopa reduces the amount of levodopa re-
quired by about 75 percent and, when adminis-
tered with levodopa, increases both plasma
levels and the plasma half-life of levodopa, and
decreases plasma and urinary dopamine and
homovanillic acid.

In clinical pharmacologic studies, simulta-
neous administration of carbidopa and
levodopa produced greater urinary excretion
of levodopa in proportion to the excretion of
dopamine than administration of the two
drugs at separate times.

Pyridoxine hydrochloride (vitamin B₆), in oral
doses of 10 mg to 25 mg, may reverse the effects
of levodopa by increasing the rate of aromatic
amino acid decarboxylation. Carbidopa inhib-
its this action of pyridoxine.

The 1 to 10 proportion of carbidopa and
levodopa in SINEMET is based on evidence
that peripheral dopa decarboxylase is satu-
rated by carbidopa at doses of approximately
70 to 100 mg per diem. SINEMET tablets pro-
vide this amount or more of carbidopa to the
majority of patients previously maintained on
levodopa then retitrated to optimal response
with the combination.

Double-blind clinical trials with a fixed dose 1
to 10 ratio of carbidopa to levodopa provide
evidence of useful effects when compared with
levodopa. However, during these clinical trials
certain patients were found to benefit from
different proportions of carbidopa and
levodopa (see DOSAGE AND ADMINIS-
TRATION).

Indications

SINEMET, a combination of carbidopa and
levodopa, is indicated in the treatment of the
symptoms of idiopathic Parkinson's disease
(paralysis agitans), postencephalitic parkin-

Continued on next page

Information on the Merck Sharp & Dohme
products listed on these pages is the full
prescribing information from package
circulars in use September 30, 1978.