Rotavirus Vaccine, Live, Oral, Tetravalent
RotaShield®

LYOPHILIZED PREPARATION FOR RECONSTITUTION AND ORAL ADMINISTRATION

NOT FOR INJECTION

TO BE SOLD ONLY AS A TWO-COMPONENT PACKAGE

Rx ONLY

DESCRIPTION

Rotavirus Vaccine, Live, Oral, Tetravalent, **RotaShield®**, when reconstituted, is a live, oral, tetravalent vaccine for use in the prevention of rotavirus gastroenteritis in infants. The vaccine contains four live viruses, a rhesus rotavirus (serotype 3) and three rhesus-human reassortant viruses (serotypes 1, 2, and 4).[1] The serotype 3 component displays strong serologic cross-reactivity with the human rotavirus serotype 3 and the reassortant components provide human serotype-specific viral protein 7 (VP7) antigens identical to those of rotavirus serotypes 1, 2, and 4. The vaccine is for protection against the four rotavirus serotypes that are responsible for the major portion of rotavirus disease in infants and young children in the US.[2,3,4]

The viruses are grown in a fetal rhesus diploid cell line (FRhL-2) using Minimum Essential Medium. The viruses and the cell line have undergone extensive testing for adventitious agents. After the rotavirus is harvested, residual cellular debris is removed by filtration. Sucrose, monosodium glutamate, potassium monophosphate, and potassium diphosphate are added to the virus-containing medium to stabilize the rotavirus. Fetal bovine serum, neomycin sulfate, and amphotericin B are present during cell culture growth but are removed before virus infection and are present in the final product at a concentration of less than 1 μg per dose. The vaccine contains no preservatives.

RotaShield is supplied in single-dose vials as a lyophilized preparation, pink in color. The solution appears yellow-orange to purple when reconstituted as directed and may contain a fine precipitate. *The vaccine is for oral administration only.* Each 2.5 mL dose is formulated to contain equal quantities (plaque forming units, pfu) of each rotavirus serotype, such that 4×10^5 pfu of total virus is present. The vaccine is formulated to contain an expected value of 4×10^5 pfu; the potency of the vaccine is maintained throughout the dating period.

RotaShield is reconstituted with an irradiated sterile citrate-bicarbonate diluent containing 9.6 mg/mL of citric acid and 25.6 mg/mL of sodium bicarbonate. The buffering action of the diluent neutralizes stomach acidity and protects the acid-labile rotaviruses from degradation.[5,6,7,8]

CLINICAL PHARMACOLOGY

Rotavirus is the single most important cause of epidemic severe acute gastroenteritis (diarrhea and vomiting) in infants and young children both in developed and developing countries.[9] It is estimated that in the United States each year 411,000 infants under one year of age and 1½ million between one and two years of age require treatment for rotaviral gastroenteritis.[2] Approximately half of these young children develop severe diarrhea.[2] In temperate climates the disease is seasonal, with a peak in the winter months. In tropical and subtropical areas it is generally endemic.[10] These differences in the pattern of disease in different parts of the world do not affect the severe nature of the disease in the infected infants. In US cities as well as in the developing world, rotavirus causes about 5% of diarrheal disease in the community but nearly 40% of the severe dehydrating illness.[2]

In the United States, 1 in 8 of all infants requires medical treatment for rotaviral gastroenteritis and 1 in 50 US infants is hospitalized for rotaviral gastroenteritis.[11] Outbreaks of rotaviral gastroenteritis have also been identified in adults; however, epidemiologic studies confirm that rotavirus gastroenteritis, especially severe rotavirus disease, occurs largely in infants younger than 2 years of age.[2] Untreated severe rotavirus diarrhea in infants can be rapidly fatal unless dehydration is corrected by oral or intravenous replacement of fluids.[2]

Rotavirus is presumed to be transmitted by the fecal-oral route.[12] Ingested virus particles infect the cells in the villi of the small intestine. Copious acute watery diarrhea occurs after an incubation period of 1 to 2 days.[2] Although there are many different strains of rotavirus, the majority of disease in the US is caused by four human serotypes of rotavirus group A, designated serotypes (G)1, 2, 3, and 4 based on the serologic response to the VP7 (G) antigen.[2]

Mechanism of Action

The immune response to natural rotavirus infection is not completely understood. Most studies indicate that protection derived from an episode of rotavirus gastroenteritis is incomplete, and that infants and children can be reinfected.[2] Studies also show that natural infection partially protects against subsequent episodes of severe illness.[2] Although reinfection occurs, it results in clinically mild or even asymptomatic disease. Data suggest that local (mucosal) immunity plays an important role in protection.[13]

The mechanism of vaccine protection is not fully understood. The live vaccine virus generates IgG antibodies that neutralize the serotype 3 parent rotavirus strain as well as human rotavirus serotypes 1, 2, 3, and 4. In addition, **RotaShield®** induces IgA antibody, which is thought to reflect a local immune response.

*Evaluation of the Clinical Efficacy of **RotaShield®***

Clinical trials were conducted in nine countries. In these studies, a total of 10,816 subjects received the vaccine at doses ranging from 10^4 pfu to 4×10^6 pfu, including 5,733 infants who received the vaccine in placebo-controlled trials. The evidence for the efficacy of **RotaShield®** in preventing rotavirus disease comes from three placebo-controlled efficacy trials, described below, in which 2,014 (1,872 evaluable) infants received 3 doses of **RotaShield** (4×10^5 pfu), by 33 weeks of age. These clinical trials included 2-month-old healthy infants, with no restriction regarding premature birth. Twenty-seven premature infants between 27 and

36 weeks of gestational age and nine premature infants with gestational age not specified received **RotaShield.**

Table 1 shows the efficacy of **RotaShield** in preventing all rotaviral gastroenteritis, in preventing severe rotaviral gastroenteritis, and in reducing the need for medical intervention (taking the infant to a doctor's office, clinic, or emergency room, including treatment by a health care professional for dehydration), because of rotavirus gastroenteritis.

RotaShield (4×10^5 pfu) was evaluated for efficacy against rotaviral gastroenteritis in three randomized, double-blind, placebo-controlled trials in the United States and Finland.[14,15,16] In all trials, the surveillance period for efficacy began two weeks after the receipt of the third vaccine dose. For the purposes of assessing efficacy against differing disease severity, severe rotaviral gastroenteritis was defined using one of two numerical scoring systems. A modification of the severity scale developed by Flores *et al.*[17] was used in Trials 1 and 2. In Trial 3 the severity scale of Ruuska and Vesikari[18] was used. In both systems, a higher score correlated with more clinically severe disease as defined by: (a) longer duration of illness for diarrhea (Trials 1 and 2, greater than 3 days; Trial 3, greater than 6 days) and vomiting (Trials 1 and 2, greater than 2 days; Trial 3, greater than 3 days); (b) increased frequency of stools per 24 hours (Trials 1 and 2, greater than 5 stools/24 hours; Trial 3, greater than 6 stools/24 hours); (c) dehydration (Trials 1 and 2, presence of dehydration; Trial 3, greater than 5% dehydration); (d) increased fever (Trials 1 and 2, greater than 38.6°C; Trial 3, greater than 38.9°C); (e) and, the need for medical intervention (Trials 1 and 2, taken to clinic, emergency room, or physician's office; Trial 3, hospitalization).

Trial 1 was a multicenter trial performed in healthy US infants. Infants were randomized to receive three doses of either **RotaShield** or placebo at approximately 2, 4, and 6 months of age (a minimum of 3 weeks separating each dose) prior to the commencement of the rotavirus season, and completed one full season of surveillance for rotaviral gastroenteritis. The primary endpoint of Trial 1 was the prevention of rotaviral gastroenteritis of any severity. The **RotaShield** group experienced a significant reduction in the incidence of: (a) all rotaviral gastroenteritis, 51/398 infants (13%) compared with 97/385 infants (25%) in the placebo group; (b) severe rotaviral gastroenteritis, 7/398 infants (2%) compared with 34/385 infants (9%) in the placebo group; and, (c) rotaviral gastroenteritis requiring medical intervention, 16/398 infants (4%) compared with 58/385 infants (15%) in the placebo group.[14]

Trial 2 was performed at multiple sites in healthy Native American infants. Infants were randomized to receive three doses of either **RotaShield** or placebo at approximately 2, 4, and 6 months of age (a minimum of 3 weeks separating each dose) prior to the commencement of the rotavirus season, and completed one full season of surveillance for rotaviral gastroenteritis. The primary endpoint of Trial 2 was the prevention of rotaviral gastroenteritis of any severity. The **RotaShield** group experienced a significant reduction in the incidence of: (a) all rotaviral gastroenteritis, 39/347 infants (11%) compared with 81/348 infants (23%) in the placebo group; (b) severe rotaviral gastroenteritis, 8/347 infants (2%) compared with 27/348 infants (8%) in the placebo group; and, (c) rotaviral gastroenteritis requiring medical intervention, 19/347 infants (5%) compared with 54/348 infants (16%) in the placebo group.[15]

Trial 3 was performed in healthy infants at multiple sites in Finland. Infants were randomized to receive three doses of either **RotaShield** or placebo at approximately 2, 3, and

5 months of age (a minimum of 3 weeks separating each dose) to be given throughout the year, and completed at least one full season of surveillance for rotaviral gastroenteritis. The primary endpoint of Trial 3 was the prevention of severe rotaviral gastroenteritis over two efficacy analysis periods. During the first year of surveillance, the **RotaShield** group experienced a significant reduction in the incidence of: (a) all rotaviral gastroenteritis, 8/537 infants (1%), compared with 47/543 infants (9%) in the placebo group; (b) the incidence of severe rotaviral gastroenteritis, 1/537 infants (less than 1%) compared with 20/543 infants (4%) in the placebo group. Over two years of surveillance, the **RotaShield** group experienced a significant reduction in the incidence of: (a) all rotaviral gastroenteritis, 54/1,127 infants (5%), compared with 172/1,146 infants (15%) in the placebo group; (b) the incidence of severe rotaviral gastroenteritis, 8/1,127 infants (1%), compared with 92/1,146 infants (8%) in the placebo group; and (c) rotaviral gastroenteritis requiring medical intervention, 14/1,127 infants (1%), compared with 78/1,146 infants (7%) in the placebo group.[16]

In Trials 1, 2, and 3, the **RotaShield** groups experienced a significant reduction in the duration of: (a) diarrhea caused by rotaviral gastroenteritis by approximately one day compared with the placebo group; and (b) vomiting caused by rotaviral gastroenteritis by approximately one-half to one day compared with the placebo group.[14,15,16]

TABLE 1. EFFICACY[a] OF **RotaShield®**

		Any Rotaviral GE[b]		Severe Rotaviral GE		Medical Intervention[c]	
Trial	Group	Incidence	Relative Efficacy[d]	Incidence	Relative Efficacy	Incidence	Relative Efficacy
1[e]	**RotaShield®**	51/398 (13%)	49[k] (31,63)	7/398[f] (2%)	80 (56,91)	16/398 (4%)	73 (54,84)
	Placebo	97/385 (25%)		34/385[f] (9%)		58/385 (15%)	
2[g]	**RotaShield®**	39/347 (11%)	52[k] (31,66)	8/347[f] (2%)	70 (35,86)	19/347 (5%)	65 (42,79)
	Placebo	81/348 (23%)		27/348[f] (8%)		54/348 (16%)	
3[h]	One Season Surveillance						
	RotaShield®	8/537 (1%)	83 (64,92)	1/537[i] (< 1%)	95[k] (63,99)	NA[j,l]	
	Placebo	47/543 (9%)		20/543[i] (4%)		NA[j,l]	
	Two Season Surveillance						
	RotaShield®	54/1127 (5%)	68 (57,76)	8/1127 (1%)	91 (82,96)	14/1127[j] (1%)	82 (69,90)
	Placebo	172/1146 (15%)		92/1146 (8%)		78/1146[j] (7%)	

a: Efficacy data are derived from first season and efficacy surveillance started 2 weeks post third dose.
b: GE, gastroenteritis.
c: Medical intervention for treatment of rotaviral GE
d: Relative efficacy is defined as [1-(rate in vaccine group/rate in placebo group)] x 100; 95% confidence intervals shown.
e: Trial 1 was the US multicenter trial. Relative efficacy was 68% for severe gastroenteritis as defined in the protocol and 80% from a post hoc analysis using the more stringent definition as in trial 2.[14]
f: A modification of the 20-point scoring system of Flores et al was used to evaluate severity of gastroenteritis.
g: Trial 2 was a two-year study conducted with Native American infants. The first year results are presented here.[15]
h: Trial 3 was a two-year study conducted in Finland. Severe rotaviral gastroenteritis was the primary endpoint.[16]
i: The 20-point scoring system of Ruuska and Vesikari[18] was used to evaluate severity of gastroenteritis.
j: In Trial 3, medical intervention was determined over 2 years of the study.
k: Primary endpoint of the trial.
l: NA, not applicable

Efficacy Against Dehydration and Hospitalization

In Trial 1, the **RotaShield** group experienced a significant reduction in the incidence of dehydration caused by rotaviral gastroenteritis, 0/398 infants (0%) compared with 13/385 infants (3%) in the placebo group. In Trial 3, the **RotaShield** group experienced a significant reduction in the incidence of dehydration caused by rotaviral gastroenteritis during the two years of the trial, 1/1127 (less than 1%) compared with 32/1127 (3%) in the placebo group.[16] In addition, vaccinated infants in these two studies who contracted rotaviral gastroenteritis had episodes that were significantly less severe than infants who received placebo.[14,15,16] In Trial 2, similar rates were observed in the incidence of dehydration caused by rotaviral gastroenteritis between the **RotaShield** group, 5/347 infants (1 %) and the placebo group, 9/348 infants (3 %).[19]

In Trial 3, the **RotaShield** group experienced a significant reduction in the need for hospitalization caused by rotavirus gastroenteritis during the two years of the trial, 0/54 infants (0%), compared with 16/72 infants (9%) in the placebo group.[16]

Summary of Clinical Efficacy

Overall, the relative efficacy of **RotaShield** against: (a) all rotaviral gastroenteritis following one season of surveillance ranged from 49% to 83%; (b) severe rotavirus gastroenteritis ranged from 70% to 95%; (c) rotaviral gastroenteritis requiring medical intervention ranged from 65% to 82%; and, (d) dehydration from 97% to 100% (Trial 1 and Trial 3).

Efficacy Through Multiple Seasons

The efficacy of **RotaShield** against severe rotaviral gastroenteritis over two seasons was evaluated in Trials 2 and 3. In Trial 2, all infants received all three doses of **RotaShield** prior to the first season of surveillance, permitting surveillance across two seasons to occur. However, in this trial there were an insufficient number of cases of rotavirus gastroenteritis in the second season in either study group to be able to determine second-season efficacy. In Trial 3, a majority of infants were immunized such that efficacy could be determined for a single season. A cohort of infants (167 infants) received all three doses of either **RotaShield** (85 infants) or placebo (82 infants) prior to the commencement of the first season of surveillance. As such, surveillance of these infants for rotaviral gastroenteritis was possible over two complete seasons. During the second year of surveillance of these 167 infants, the **RotaShield** group experienced a significant reduction in the incidence of severe rotaviral gastroenteritis 2/85 infants (2%) compared with 11/82 infants (13%) in the placebo group. This reflects a second-season efficacy against severe gastroenteritis of 83%.

The results obtained from Trial 3 showed **RotaShield** to be effective through a second season for preventing rotaviral gastroenteritis in infants.[20]

Efficacy Against Disease Caused by Different Serotypes

RotaShield® was designed specifically to help protect infants from illness caused by the four human rotavirus serotypes (G types 1, 2, 3, and 4). These four serotypes cause the majority of rotavirus disease in infants and young children in the US.[2,3,4] **RotaShield** has been proven effective against the serotypes of rotavirus (G 1, 3, and 4) that were circulating at the time of the clinical trials.[15,20]

Transmission

RotaShield® is a live virus vaccine that replicates in the intestine of the recipient and is shed in the stool.[21] In one clinical trial,[22] approximately half of the subjects who received **RotaShield** shed vaccine virus in at least one stool collected between 3 and 5 days after vaccination.

Although numerous studies in day-care centers[21,23,24,25,26] failed to demonstrate transmission of vaccine strains from vaccine recipients to nonrecipients, low level transmission was detected in a study conducted in Venezuela by using a highly sensitive method (polymerase chain reaction).[27] These vaccine components did not appear to cause illness, and in every case where diarrhea was detected, wild-type virus was found in addition to vaccine virus.

Effect of Breast-Feeding

Although antibodies to rotavirus may be detected in breast milk, based on the available data, there is no evidence the efficacy of **RotaShield** is reduced when administered to breast-fed infants.[14, 20,28] **RotaShield** can be administered to infants who are breast-fed exclusively or partly. Moreover, there is currently no recommendation for a delay in the administration of the vaccine after breast-feeding.

INDICATIONS AND USAGE

RotaShield® is indicated for the prevention of gastroenteritis caused by those rotavirus serotypes contained in the vaccine. The recommended dosing schedule for oral immunization with **RotaShield** in infants is at 2, 4, and 6 months of age. The first dose may be administered as early as 6 weeks of age, with subsequent doses at least 3 weeks apart. In clinical trials infants have received the third dose at up to 33 weeks of age with no increased adverse reactions. Because infants older than 6 months may have an increased risk of fever subsequent to administration of the first dose of vaccine, initiation of vaccination after the age of 6 months is currently not recommended.

No data are available on the degree of protection provided if only one or two doses are given. Also, **RotaShield** does not protect 100% of individuals receiving the vaccine.

RotaShield does not protect against non-rotaviral diarrhea. Diarrhea due to other infections and non-infectious causes can still occur. There are no data to indicate whether **RotaShield** may protect against rotaviral diarrhea caused by strains not contained in the vaccine (strains other than [G] 1, 2, 3, and 4).

Under no circumstances is this vaccine to be administered parenterally.

CONTRAINDICATIONS

FOR ORAL ADMINISTRATION ONLY

Under no circumstances should this product be administered parenterally.

Hypersensitivity to any component of the vaccine, such as aminoglycoside antibiotics, monosodium glutamate, or amphotericin B, is a contraindication to the use of **RotaShield®**.

Immunocompromised individuals may shed rotavirus for prolonged periods, and the safety and efficacy of RotaShield has not been studied in these populations. Therefore, until studies are conducted and data become available, RotaShield is contraindicated in patients with known or suspected immune deficiency diseases and conditions such as combined immunodeficiency, hypogammaglobulinemia, agammaglobulinemia, human immunodeficiency virus (HIV) infection, thymic abnormalities, malignancy, leukemia, lymphoma, or advanced debilitating conditions. Further, it is also contraindicated in patients who may be immunosuppressed or have an altered or compromised immune status, such as those who are being treated with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies. The frequency and route of administration of corticosteroids, the underlying disease and concurrent other therapy also are factors affecting immunosuppression. Most experts agree that steroid therapy usually does not contraindicate administration of a live virus vaccine when it is short term (i.e., <2 weeks); low to moderate dose; long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection.[29] The clinical judgment of the attending physician should prevail at all times.

RotaShield is contraindicated in patients who have on-going diarrhea or vomiting.

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Although a severe or even a moderate febrile illness is sufficient reason to postpone vaccinations, minor illnesses, such as a mild upper respiratory infection with or without low-grade fever, are not generally contraindications.[30,31,32]

WARNINGS

Do not administer RotaShield® parenterally.

Vaccine virus may be transmitted from vaccine recipients to non-recipients (see **CLINICAL PHARMACOLOGY**, *Transmission* section). Do not administer to immunosuppressed infants. For infants who live in households with an immunosuppressed family member, see **PRECAUTIONS**, *General*.

Health care professionals should administer **RotaShield** with caution to patients with a possible history of latex sensitivity, since its packaging contains dry natural rubber.

PRECAUTIONS

General

Because live virus vaccines can be transmitted to nonvaccinated contacts, close association between high risk individuals, e.g. immunocompromised persons, and **RotaShield®** vaccine recipients should be avoided whenever possible, for up to 4 weeks. In circumstances where contact with high risk individuals is unavoidable, the potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus. [See **CLINICAL PHARMACOLOGY**, *Transmission*]

Care is to be taken by the health care provider for safe and effective use and appropriate handling of **RotaShield**. Prior to administration of **RotaShield**, the parent or guardian should be asked about the personal history, family history, and recent health status of the patient. The health care provider should ascertain previous immunization history and current health status, including immune status of the patient and family members to determine the existence of any contraindications to immunization with **RotaShield**. The health care provider should question the parent or guardian about reactions to a previous dose of **RotaShield**.

As with any biological product, before administration of **RotaShield**, the physician should take all known precautions for prevention of allergic or any other reactions. This includes a review of the patients history for possible sensitivity, the ready availability of epinephrine (1:1000) and other appropriate agents used for control of immediate allergic reactions, and a knowledge of the recent literature pertaining to the use of the biologic concerned, including the nature of the side effects and adverse reactions which may follow its use.

Data are insufficient to establish the safety and efficacy of **RotaShield** in premature infants less than 37 weeks gestation. Moreover, it is not known whether premature infants are at higher risk for rotavirus hospitalization when compared with full-term infants. Until such data become available, physicians should individually weigh the potential benefits and risks of administering **RotaShield** to a premature infant.

Packaging for **RotaShield** contains dry natural rubber. Health care professionals should administer **RotaShield** with caution to patients with a possible history of latex sensitivity.

Information for Parents/Guardians

Prior to administration of this vaccine, health care personnel should inform the parent, guardian, or other responsible adult, of the benefits and risks to the patient (see **ADVERSE REACTIONS** and **WARNINGS** sections) , and the importance of completing the immunization series. Parents or guardians should be instructed to use proper hand-washing techniques at the time of diaper changes. Parents or guardians should be instructed to report any serious adverse reactions to their health care provider. The health care provider should provide vaccine information statements, once available, at the time of each vaccination.

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[33] The toll-free number for VAERS forms and information is 1-800-822-7967.

Laboratory Tests

Stools excreted during the week after vaccination with **RotaShield** may test positive by commercial assay for rotavirus due to the presence of vaccine virus.

Drug Interactions

Information is not available regarding the administration of **RotaShield** to individuals who have recently received immune globulin-containing products either orally or parenterally. Studies have shown that coadministration of **RotaShield** with oral poliovirus vaccine (OPV), diphtheria-tetanus-whole-cell pertussis (DTP), and *Haemophilus influenzae* type b (Hib) vaccines does not interfere with the immune response to any of these vaccines (see **DOSAGE AND ADMINISTRATION**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

RotaShield has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with **RotaShield**. It is also not known whether **RotaShield** can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. **RotaShield** is not recommended for use in pregnant women.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

Pediatric Use

RotaShield has been shown to be usually well-tolerated and immunogenic in infants. See **DOSAGE AND ADMINISTRATION** for the recommended pediatric dosage.

ADVERSE REACTIONS

In eight studies,[15,16,22,34,35,36,37] 6,948 infants received **RotaShield®** and 2,222 received placebo (9,170 infants in all). This includes 2,208 infants who received **RotaShield** in five placebo-controlled studies[14,15,16,34,35] and 4,740 infants who received it in three studies that were not placebo-controlled.[22, 36,37]

In the clinical studies, parents were asked to record the type and number of stools and the infant's temperature, and to note the presence or absence of the following symptoms: vomiting, abdominal cramping, decreased appetite, coughing, runny nose, wheezing, irritability, and changes in activity. In the five placebo-controlled studies, fever greater than 38°C (100.4°F), fever greater than 39°C (102.2°F), decreased appetite, irritability, and decreased activity were reported more in the vaccinated infants than in the placebo recipients during the five days after the first dose. Fever greater than 38°C/ 100.4°F was observed more in vaccinated infants than in placebo recipients in the five days after the second dose. No differences were observed in the incidence of any of the solicited symptoms in the five days after the third dose. These differences are summarized in Table 2.

In the five placebo-controlled studies, the rate of diarrhea occurring in the first five days following a dose of **RotaShield** or placebo was similar and not statistically significant. In Trial 3, a greater number of infants who received **RotaShield** experienced three or more looser than normal stools in a twenty-four hour period following receipt of the first vaccine dose (34/1,184 infants; 3%) compared with placebo recipients (15/1,150 infants; 1%). These rates were similar or lower than seen following the first dose of either **RotaShield** or placebo in Trials 1 and 2 (7% each).

TABLE 2. SUMMARY OF SOLICITED SYMPTOMS WHICH WERE OBSERVED WITHIN 5 DAYS[a,b] AFTER EACH DOSE FOR WHICH THERE WERE DIFFERENCES BETWEEN VACCINE ($4x10^5$ pfu) AND PLACEBO RECIPIENTS IN INCIDENCE AFTER AT LEAST ONE DOSE: NUMBER (%) OF INFANTS[c]

	Dose 1		Dose 2		Dose 3	
Symptom	**RotaShield®**	Placebo	**RotaShield®**	Placebo	**RotaShield®**	Placebo
Temperature > 38° C /100.4°F	461/2153 (21)[d]	124/2164 (6)	218/1983 (11)[e]	181/2002 (9)	273/1918 (14)	250/1920 (13)
Temperature > 39° C /102.2°F	37/2153 (2)[d]	12/2164 (1)	22/1983 (1)	14/2002 (1)	42/1918 (2)	28/1920 (1)
Decreased appetite	375/2181 (17)[d]	238/2191 (11)	226/2017 (11)	236/2038 (12)	269/1954 (14)	236/1965 (12)
Irritability	541/1317 (41)[d]	428/1336 (32)	486/1272 (38)	507/1292 (39)	446/1232 (36)	443/1262 (35)
Decreased activity	436/2179 (20)[d]	292/2190 (13)	238/2018 (12)	244/2036 (12)	203/1952 (10)	212/1965 (11)

a: Day 1 was the day of vaccination.
b: Symptom occurred at least once during the 5-day period.
c: Placebo-controlled trials only.
d: $p < 0.001$, **RotaShield®** vs placebo.
e: $0.01 < p < 0.05$, **RotaShield®** vs placebo.

The parents were also asked to report any adverse events that occurred at other times during the study. In the five placebo-controlled studies, the incidence of adverse events for the vaccinated subjects was the same as that for the placebo recipients with the exception of fever, which occurred more frequently in vaccinated subjects than in placebo recipients: 151 of 2,208 infants who received **RotaShield** (6.8%) had fever greater than 38 °C (100.4 °F), compared with 117 of 2,222 infants (5.3%) who received placebo. This difference was statistically significant.

In addition to the solicited symptoms noted in Table 2, parents also reported the following events which occurred during the course of eight clinical trials, in 1% or more of the 6948 infants who received **RotaShield**. These events are listed below in decreasing order of frequency without regard to causality: otitis media, infection, bronchitis, conjunctivitis, flu syndrome, fever, bronchiolitis, increased cough, pneumonia, gastroenteritis, pharyngitis, asthma, rhinitis, rash, dyspepsia, and eczema.

Severe symptoms of gastroenteritis were seen within 30 days after vaccination in less than 0.1% of infants who received vaccine or placebo: 3 of the 6,948 infants who received **RotaShield** and 2 of the 2,222 infants who received placebo.[38]

Other events that have occurred rarely (< 1%) during the course of eight clinical trials in 6,948 **RotaShield** recipients include meningitis, hepatitis, and seizures, of which the rate observed among vaccinees was less than that seen in placebo recipients.

Intussusception was noted in 5 of 10,054 (0.05%) vaccine recipients compared to 1 of 4,633 (0.02%) placebo recipients. These rates of intussusception were not statistically significantly different and the rate observed among vaccinees was similar to that seen in comparison populations.[39] Failure to thrive /growth delay was observed in **RotaShield** recipients (18/6,948 infants; 0.3%) and in placebo recipients (6/2,222 infants; 0.3%). Upon blinded expert review of all cases, most were found to be consistent with normal growth rate variations; five cases (3 vaccine, 2 placebo) were thought to represent abnormal growth delays. No causal relationship has been established for these adverse events and administration of **RotaShield**. Five deaths (5/6,948 infants; 0.07%) occurred among the subjects who received **RotaShield**; a similar incidence was seen among the placebo recipients (2/2,222 infants; 0.09%).

DOSAGE AND ADMINISTRATION:

FOR ORAL ADMINISTRATION ONLY

UNDER NO CIRCUMSTANCES IS ROTASHIELD® TO BE ADMINISTERED PARENTERALLY.

Vaccination Schedule

The immunization series consists of three 2.5-mL doses of **RotaShield®** administered orally to infants. The recommended dosing schedule for oral immunization with **RotaShield** in infants is at 2, 4, and 6 months of age. The first dose may be administered as early as 6 weeks of age, with subsequent doses at least 3 weeks apart. In clinical trials infants have received the third dose at up to 33 weeks of age with no increased adverse reactions. Because infants older than 6 months may have an increased risk of fever subsequent to administration of the first dose of vaccine, initiation of vaccination after the age of 6 months is currently not recommended.

Use With Other Vaccines

Specific studies evaluated the immune responses to OPV and to whole-cell DTP and Hib vaccines when these vaccines were coadministered with **RotaShield®**. Three studies evaluated the antibody levels to the OPV serotypes when OPV and **RotaShield** were administered concomitantly, [14,40,41,42] and a fourth study [34] investigated whether there might be possible interference between **RotaShield** and DTP or Hib. The concomitant administration of **RotaShield** does not interfere with the immune response to these routinely recommended childhood vaccines. Data are not available for other childhood vaccines. Additional studies are ongoing.

OPV

In a large multicenter trial, children who were given OPV concurrently with **RotaShield** developed detectable antibody to all 3 serotypes of poliovirus. **RotaShield** did not interfere with the immune response to any OPV serotype. [14,40] In addition, the concomitant administration of **RotaShield** and OPV had no effect on the protective efficacy of **RotaShield** [14,40] when all three doses of **RotaShield** were administered.

Whole-Cell DTP and Hib

Another study[34] evaluated the possibility of interference between **RotaShield** and the DTP and Hib vaccines. The study vaccine groups were compared for immune responses to diphtheria toxoid, tetanus toxoid, *Bordetella pertussis,* and *H. influenzae* type b when the DTP and Hib vaccines were coadministered with **RotaShield**. The immune responses to the DTP and Hib vaccines were unaffected by the concomitant administration of **RotaShield**.

Dose Administration

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination. Repeat dosing is not indicated if an infant should regurgitate vaccine.

Each single oral dose of **RotaShield®** is approximately 2.5 mL in volume. The dose is provided in two parts: a 5-mL screw-cap vial containing the lyophilized vaccine and a Dispette® assembly in a foil pouch containing the buffer diluent for reconstitution of the vaccine. Only the specific buffer diluent provided is to be used for reconstitution. If the integrity of either the vaccine vial or the pouch of buffer diluent has been compromised, that particular vial or pouch must be discarded.

To reconstitute, squeeze the contents of the Dispette into the vial containing the vaccine. Resuspension is instantaneous. The solution will appear yellow-orange to purple and may contain a fine precipitate. Draw the contents back into the Dispette. Place the Dispette with the vaccine into the child's mouth and slowly squeeze out the entire contents. [See pictorial diagram below.]

Ideally, the vaccine should be administered immediately after reconstitution. However, the Dispette containing the reconstituted vaccine can be recapped and administration delayed for up to 60 minutes at room temperature (23°C to 27° C; 73°F to 81°F) or up to 4 hours at refrigeration temperature (2°C to 8°C; 36°F to 46°F). Discard the reconstituted vaccine if it has not been administered within these time points.

HOW SUPPLIED

RotaShield® is supplied as follows:

1) One carton containing 12 single-dose vials of lyophilized Rotavirus Vaccine, Live, Oral, Tetravalent, **RotaShield®** (NDC 0008-0847), and 12 filled Dispettes® each containing 2.5 mL of buffer diluent for rotavirus vaccine (NDC 0008-1163). Combination package NDC number 0008-2562-01.
2) One carton containing 50 single-dose vials of lyophilized Rotavirus Vaccine, Live, Oral, Tetravalent, **RotaShield®** (NDC 0008-0847), and 50 filled Dispettes® each containing 2.5 mL of buffer diluent for rotavirus vaccine (NDC 0008-1163). Combination package NDC number 0008-2562-02.

A unit dose consists of one vial of lyophilized vaccine formulated to contain 4×10^5 pfu total virus, and one pouch of buffer diluent, 2.5 mL in volume, containing 9.6 mg/mL of citric acid and 25.6 mg/mL of sodium bicarbonate. The vaccine and diluent do not contain preservatives. Proper handling and storage before and after reconstitution are essential (see *STORAGE, below).*

STORAGE

DO NOT FREEZE THE VACCINE OR THE DILUENT.

The lyophilized vaccine and diluent should be stored at room temperature below 25°C (77°F). The lyophilized vaccine and diluent may also be refrigerated (2°C to 8°C; 36°F to 46°F).

The reconstituted vaccine is stable in the Dispette® for up to 60 minutes at room temperature (23°C to 27°C; 73°F to 81°F) and up to 4 hours at refrigeration temperature (2°C to 8°C; 36°F to 46°F), after which the reconstituted product must be discarded.

The product must be used before the expiration date.

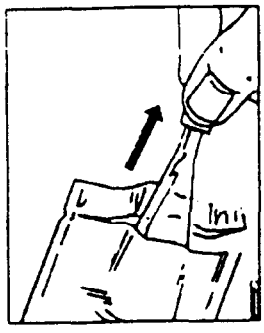
Provided the vaccine is properly stored, the vaccine retains an expected value of 4×10^5 pfu throughout the dating period.

Manufactured by:
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
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RotaShield® Administration Instructions

Instructions for reconstitution

Figure 1. Tear off top of foil pouch and remove Dispette® containing buffering diluent.

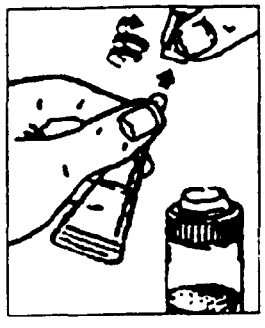


Figure 2. Unscrew the cap from the vial containing the lyophilized **RotaShield®** vaccine. Twist cap off of Dispette. (Retain cap to recap Dispette after reconstitution.)

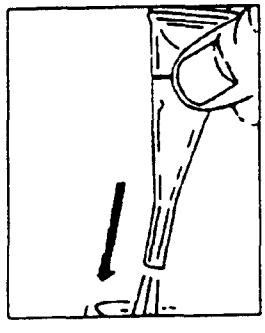


Figure 3. Squeeze entire contents of Dispette (diluent) into the vial containing lyophilized **RotaShield** vaccine.

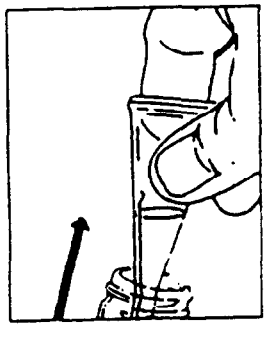
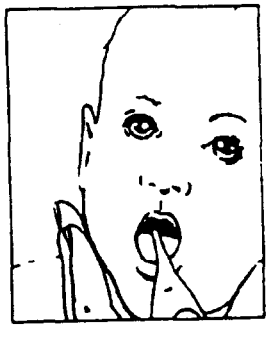


Figure 4. After reconstitution of the vaccine, squeeze empty Dispette and insert into pool of liquid vaccine. Withdraw reconstituted vaccine back into Dispette, by releasing hold on the Dispette. Recap Dispette until administration of the vaccine.



Administration

Figure 5. Remove cap. Administer vaccine by placing the Dispette into the child's mouth and slowly squeezing out the entire contents of Dispette.

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