PRODUCT MONOGRAPH

PRIORIX-TETRA

Combined measles, mumps, rubella and varicella vaccine, live, attenuated

Lyophilized powder for injection

Active immunizing agent

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Combined measles, mumps, rubella and varicella vaccine, live, attenuated

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength per 0.5 mL dose	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection (SC) or Intramuscular injection (IM)	Lyophilized powder for injection / Live, attenuated measles virus (Schwarz strain) not less than $10^{3.0}$ $CCID_{50}$ Live, attenuated mumps virus (RIT 4385 strain, derived from Jeryl Lynn strain) not less than $10^{4.4}$ $CCID_{50}$ Live, attenuated rubella virus (Wistar RA 27/3 strain) not less than $10^{3.0}$ $CCID_{50}$ Live, attenuated varicella virus (Oka strain) not less than $10^{3.3}$ PFU	Amino acids, lactose, mannitol, sorbitol, and water for injection. Residue: neomycin sulphate.

DESCRIPTION

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) is a lyophilized mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain), Wistar RA 27/3 rubella and Oka varicella strains of viruses.

INDICATIONS AND CLINICAL USE

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) is indicated for active immunization against measles, mumps, rubella and varicella in individuals from 9 months to 6 years of age. Efficacy has not been evaluated in subjects above 6 years of age.

PRIORIX-TETRA may be used in individuals up to 12 years of age based upon previous experience with the separate component vaccines, PRIORIX (combined measles, mumps and rubella vaccine, live, attenuated) and VARILRIX [varicella virus vaccine, live, attenuated (OKA-strain)].

CONTRAINDICATIONS

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) is contraindicated in:

- subjects with known hypersensitivity to neomycin or to any other component of the vaccine (for egg allergy, see WARNINGS AND PRECAUTIONS). A history of contact dermatitis to neomycin is not a contraindication. For a complete listing of excipients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.

- subjects having shown signs of hypersensitivity after previous administration of measles, mumps, rubella and/or varicella vaccines.

- pregnant women. Pregnancy should be avoided for one month after vaccination (see WARNINGS AND PRECAUTIONS, Special Populations).

- subjects with severe humoral or cellular (primary or acquired) immunodeficiency (see also WARNINGS AND PRECAUTIONS)

WARNINGS AND PRECAUTIONS

General

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) **must not** be administered intravascularly or intradermally.

As with other vaccines, the administration of PRIORIX-TETRA should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they can inactivate the attenuated viruses in the vaccine.

Limited protection against measles may be obtained by vaccination up to 72 hours after exposure to natural measles.

Infants in their first year of life may not respond sufficiently to the measles component of the vaccine, due to the possible persistence of maternal measles antibodies. Additional doses of a measles containing vaccine should be given according to official recommendations.

There is an increased risk of fever and febrile convulsions 5 to 12 days after the first dose of PRIORIX-TETRA as compared with 2 separate injections of MMR and varicella vaccines (see "Adverse Reactions"). There was no indication of an increased risk after the second dose.

Fever rates are usually high after the first dose of measles-containing vaccines. Vaccination of subjects with a history of febrile convulsions or a family history of convulsions should be considered with caution. Alternative immunization of these subjects with separate MMR and varicella vaccines should be considered for the first dose. In any case vaccinees should be monitored for fever during the risk period.

Transmission of measles, mumps and rubella viruses from vaccinees to susceptible contacts has never been documented, although pharyngeal excretion of the rubella virus is known to occur about 7 to 28 days after vaccination with peak excretion around the 11^{th} day. Transmission of the Oka vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees with rash. Transmission of the Oka vaccine from a vaccinee who does not develop a rash to seronegative contacts cannot be excluded.

The measles and mumps components of the vaccine are produced in chick embryo cell culture and may therefore contain traces of egg protein. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g. generalized urticaria, swelling of the mouth and throat, difficulty breathing, hypotension or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after vaccination, although these types of reactions have been shown to be very rare. Individuals who have experienced anaphylaxis after egg ingestion should be vaccinated with extreme caution, with adequate treatment for anaphylaxis on hand should such a reaction occur.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Immune

As with any vaccine, a protective immune response may not be elicited in all vaccinees. As for other varicella vaccines, cases of varicella disease have been shown to occur in persons who have previously received PRIORIX-TETRA. These breakthrough cases are usually mild, with a fewer number of lesions and less fever as compared to cases in unvaccinated individuals.

Cases of worsening of thrombocytopenia and recurrence of thrombocytopenia in subjects who suffered thrombocytopenia after the first dose have been reported following vaccination with live measles, mumps and rubella vaccines. In such cases, the risk-benefit of immunising with PRIORIX-TETRA should be carefully evaluated.

There are limited data on the use of PRIORIX-TETRA in immunocompromised subjects, therefore vaccination should be considered with caution and only when, in the opinion of the physician, the benefits outweigh the risks

Immunocompromised subjects who have no contraindication for this vaccination (see CONTRAINDICATIONS) may not respond as well as immunocompetent subjects, therefore some of these subjects may acquire measles, mumps, rubella or varicella despite appropriate vaccine administration. Immunocompromised subjects should be monitored carefully for signs of measles, mumps, rubella and varicella.

Very few reports exist on disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.

Special Populations

Pregnant Women: Pregnant women must not be vaccinated with PRIORIX-TETRA. Pregnancy should be avoided for one month after vaccination. Women who intend to become pregnant should be advised to delay pregnancy.

Adequate human data on the use of PRIORIX-TETRA during pregnancy are not available and animal studies on reproductive toxicity have not been conducted.

Nursing Women: Adequate human data on the use of PRIORIX-TETRA during lactation are not available.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety profile presented below is based on data from more than 6,700 doses of PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) administered subcutaneously to children from 9 to 27 months of age. Events were recorded for up to 42 days after vaccination.

Very Common Clinical Trial Adverse Drug Reactions ≥ 1/10

General disorders and administration site conditions: pain and redness at the injection site, fever (rectal ≥ 38°C and ≤ 39.5°C; axillary/oral: ≥ 37.5°C and ≤ 39°C)

Common Clinical Trial Adverse Drug Reactions ≥ 1/100 to < 1/10

General disorders and administration site conditions: swelling at the injection site, fever (rectal > 39.5°C; axillary/oral > 39°C)*

* Following the administration of the first dose of PRIORIX-TETRA, higher incidences of fever (approximately 1.5 fold) were observed when compared to the concomitant administration of PRIORIX and VARILRIX vaccines at separate injection sites.

Psychiatric disorders: irritability

Skin and subcutaneous tissue disorders: rash including measles-like, rubella-like and varicella-like rash

Uncommon Clinical Trial Adverse Drug Reactions ≥ 1/1,000 to < 1/100

Blood and lymphatic system disorders: lymphadenopathy

Gastrointestinal disorders: parotid gland enlargement, diarrhea, vomiting

General disorders and administration site conditions: lethargy, malaise, fatigue

Infections and infestations: upper respiratory tract infection

Metabolism and nutrition disorders: anorexia

Psychiatric disorders: crying, insomnia, nervousness

Respiratory, thoracic and mediastinal disorders: rhinitis

Rare Clinical Trial Adverse Drug Reactions ≥ 1/10,000 to < 1/1,000

General disorders and administration site conditions: injection site bruising

Infections and infestations: otitis media

Nervous system disorders: febrile convulsions

Respiratory, thoracic and mediastinal disorders: cough, bronchitis

Post-Market Adverse Drug Reactions

The following post-market safety information is of the separate components of the vaccines, PRIORIX (combined measles, mumps and rubella vaccine, live, attenuated) and VARILRIX [varicella virus vaccine, live, attenuated (OKA-strain)].

The safety of measles-mumps-rubella and varicella vaccines has been well characterised in clinical trials and post-marketing surveillance. PRIORIX and VARILRIX have been used in Canadian market since 2002 and 2003 respectively. Over 144 million doses of PRIORIX and 14 million doses of VARILRIX have been distributed worldwide since 1997 and 1994 respectively. No safety concerns outside the recognized and reported safety profile has been identified to date.

Because these reactions were reported spontaneously, it is not possible to reliably estimate their frequency.

During post-marketing surveillance, the following additional reactions have been reported rarely after measles-mumps-rubella and varicella vaccination:

Blood and lymphatic system disorders: thrombocytopenia, thrombocytopenic purpura

Immune system disorders: allergic reactions (including anaphylactic and anaphylactoid reactions)

Infections and infestations: meningitis, herpes-zoster, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis and parotitis)

Musculoskeletal and connective tissue disorders: arthralgia, arthritis

Nervous system disorders: encephalitis, cerebrovascular accident, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), Guillain Barré syndrome, transverse myelitis, peripheral neuritis

Skin and subcutaneous tissue disorders: erythema multiforme, varicella-like rash

Vascular disorders: vasculitis (including Henoch Schonlein purpura and Kawasaki syndrome)

Post-Marketing Observational Safety Surveillance Study

The risk of febrile convulsions (FC) following the first dose vaccination of children aged 9 to 30 months with PRIORIX-TETRA compared with a matched cohort who received MMR or simultaneous, but separate MMR and varicella vaccination was assessed in a retrospective database analysis.

The study included 82,656 children immunized with MMRV, 149,259 with MMR and 39,203 with separate MMR and varicella vaccines. In the matched cohort, there were 82,436 subjects in the PRIORIX-TETRA group and 82,469 in the control group (pooled groups of MMR and MMR+V).

The attributable risk of febrile convulsions on cohorts matched for confounding factors (gender, age at immunization, calendar month of immunization and statutory health

insurances) in the main risk period of 5 to 12 days following first dose of PRIORIX-TETRA was 3.64/10,000 (95% CI: -6.11; 8.30). This suggests one additional case of febrile convulsion per 2,747 subjects vaccinated with PRIORIX-TETRA compared to matched control cohorts who received MMR or simultaneous, but separate MMR and varicella vaccination (FC Jacobsen case definition to identify febrile convulsions). The relative risks of febrile convulsions (FC Jacobsen case definition) for the comparison of PRIORIX-TETRA with the pooled exposure group of children vaccinated against MMR or MMR+V were 1.48 (95% CI, 1.08 - 2.01) for the entire risk period 0-30 days, and 2.43 (95% CI, 1.46 - 4.04) for the main risk period 5 to 12 days after immunization.

The study found a 4.1-fold (95% CI, 1.34 -12.68) and 3.5-fold (95% CI, 0.66 - 18.98) increase in the cumulative incidence of the main outcome 'FC narrow' in the main risk interval 5 days to 12 days after a first dose immunization with PRIORIX-TETRA compared to matched cohorts of MMR and MMR+V, respectively, and taking into account additional confounding factors (personal history of febrile convulsions, co-administration of other vaccines, and hospitalization for infectious diseases).

DRUG INTERACTIONS

Administration with Other Vaccines

Clinical studies have demonstrated that PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) can be given with any of the following monovalent or combination vaccines: hexavalent vaccines (DTaP-HBV-IPV-Hib), diphtheria-tetanus-acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), Hepatitis B vaccine (HBV). The immune response to PRIORIX-TETRA is not decreased by co-administration with any of the following vaccines: BEXSERO [meningococcal serogroup B vaccine (MenB)], meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (MenACWY) and 10-valent pneumococcal conjugate vaccine (PCV).

As higher percentages of subjects reported systemic reactions, including fever, change in eating habits, tenderness at the injection site and irritability, following BEXSERO given concomitantly with routine vaccines than after BEXSERO alone, separate vaccinations can be considered when possible.

See Part II CLINICAL TRIALS **Administration of PRIORIX-TETRA with other vaccines** and Product Monograph of the co-administered vaccine.

If PRIORIX-TETRA is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Drug-Drug Interactions
In subjects who have received human gammaglobulins or a blood transfusion, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired antibodies.

Salicylates should be avoided for 6 weeks after each vaccination as Reye's Syndrome has been reported following the use of salicylates during natural varicella infection.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
If tuberculin testing has to be done it should be carried out before or simultaneously with vaccination since it has been reported that combined measles, mumps and rubella vaccines may cause a temporary depression of tuberculin skin sensitivity. As this anergy may last up to a maximum of 6 weeks, tuberculin testing should not be performed within that period after vaccination to avoid false negative results.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
Primary immunization consists of two doses of PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) vaccine. An interval of at least 6 weeks between doses is preferable and in no circumstances should this interval be less than 4 weeks.

If official recommendations call for a second dose of varicella, PRIORIX-TETRA can be used in lieu of separate MMR and varicella vaccines. Refer to the Canadian Immunization Guide for current recommendations.

Administration
PRIORIX-TETRA is to be injected subcutaneously (SC), or intramuscularly (IM) in the deltoid region of the upper arm.

The vaccine should be administered subcutaneously in subjects with bleeding disorders (eg. thrombocytopenia or any coagulation disorder).

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they can inactivate the attenuated viruses in the vaccine.

Directions for Reconstitution

The diluent and reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the diluent or reconstituted vaccine.

The colour of the reconstituted vaccine may vary from clear peach to fuchsia pink (bright pink) due to minor variations of its pH. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, do not administer the vaccine.

Instructions for reconstitution of the vaccine with diluent presented in ampoules

PRIORIX-TETRA is reconstituted by adding the entire contents of the supplied ampoule of diluent to the vial containing the powder. The mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly.

Withdraw the entire contents of the vial.

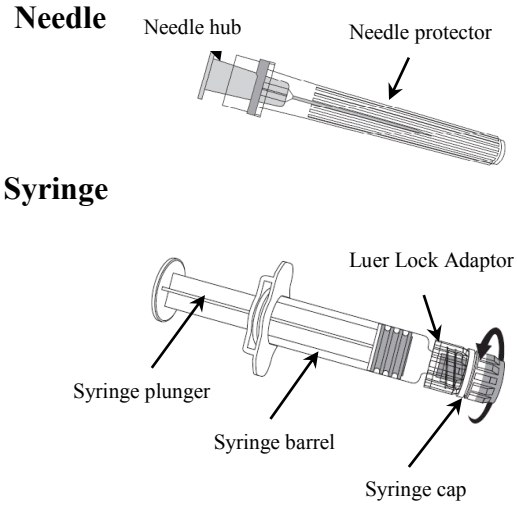
A new needle should be used to administer the vaccine.

Instructions for reconstitution of the vaccine with diluent presented in pre-filled syringe*

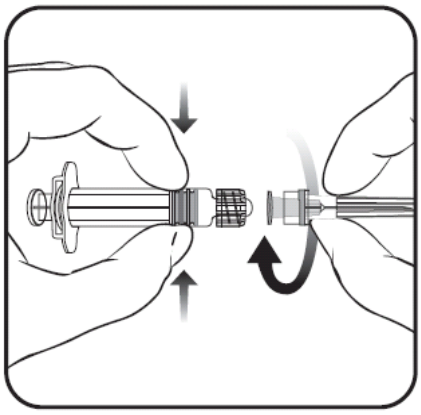
PRIORIX-TETRA must be reconstituted by adding the entire contents of the pre-filled syringe of diluent to the vial containing the powder.

To attach the needle to the syringe, carefully read the instructions given with pictures 1 and 2.

Note: The syringe provided with PRIORIX-TETRA might be slightly different (without screw thread) than the syringe illustrated. In that case, the needle should be attached without screwing.



Picture 1



Picture 2

Always hold the syringe by the barrel, not by the syringe plunger or the Luer Lock Adaptor (LLA), and maintain the needle in the axis of the syringe (as illustrated in picture 2). Failure to do this may cause the LLA to become distorted and leak.

During assembly of the syringe, if the LLA comes off, a new vaccine dose (new syringe and vial) should be used.

1. Unscrew the syringe cap by twisting it anticlockwise (as illustrated in picture 1).

2. Attach the needle to the syringe by gently connecting the needle hub into the LLA and rotate a quarter turn clockwise until you feel it lock (as illustrated in picture 2).

3. Remove the needle protector, which may be stiff.

4. Add the diluent to the vial of powder. The mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly.

5. Withdraw the entire contents of the vial.

6. A new needle should be used to administer the vaccine. Unscrew the needle from the syringe and attach the injection needle by repeating step 2 above.

Reconstituted vaccine should be injected as soon as possible, within 8 hours of reconstitution if it is stored refrigerated (2 to 8°C).

Any unused product or waste material should be disposed of in accordance with local requirements.

**Format not available in Canada*

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Measles

Measles is the most contagious vaccine-preventable infection in humans. The disease is spread by airborne or droplet exposure. There has been a marked reduction in incidence in countries where vaccine has been widely used. Complications such as otitis media and bronchopneumonia occur in about 10% of the reported cases. Measles encephalitis occurs in approximately 1 of every 1,000 reported cases and may result in permanent brain damage. In Canada, death is estimated to occur once in 3,000 cases.

Before the introduction of the vaccine, there were between 300,000 to 400,000 cases occurring annually. In Canada, since the introduction of the two doses of measles in the routine immunization schedule in every province and territory in 1997, endemic measles appears to have been eliminated.

Canadian epidemiological data for measles are available on the Public Health Agency of Canada website: http://www.phac-aspc.gc.ca/im/vpd-mev/measles-rougeole-eng.php

Mumps

Mumps is an acute infectious disease caused by the mumps virus. Before the widespread use of mumps vaccine, mumps was a major cause of viral meningitis. Since the licensure of vaccine in 1969, the number of reported mumps cases in Canada has decreased > 99%. The number of cases ranged from 402 in 1995 to 90 in 1999 with average of 237 per year. Children < 5 years accounted for 17% of cases and those aged 4 to 14 years accounted for 44%.

Canadian epidemiological data for mumps are available on the Public Health Agency of Canada website: http://www.phac-aspc.gc.ca/im/vpd-mev/mumps-eng.php

Rubella

Rubella is a viral disease that results in a transient exanthematous rash, post auricular or suboccipital lymphadenopathy, arthralgia and low grade fever. The main goal of immunization is the prevention of rubella infection in pregnancy which may give rise to congenital rubella syndrome (CRS). The risk of fetal damage following maternal infection is particularly high in the earliest months after conception (85%) in the first trimester. Since the introduction of an immunization program for rubella in Canada, reported cases of CRS have dropped throughout the country.

Canadian epidemiological data for rubella are available on the Public Health Agency of Canada website: http://www.phac-aspc.gc.ca/im/vpd-mev/rubella-eng.php

Varicella

Varicella zoster virus (VZV) causes a primary illness chickenpox, established latency in the sensory nerve ganglia and may be reactivated later as herpes zoster (shingles). VZV is spread by direct contact with the virus shed from skin lesions or in oral secretions as well as by the airborne route. The lifetime risk of developing varicella is 95% and having at least one reactivation to herpes zoster is 15 to 20%. The case fatality rates for varicella are highest among young adults. In Canada, 71% of the 59 reported chickenpox deaths from 1987 to 1997 occurred in those >15 years of age.

Canadian epidemiological data for varicella are available on the Public Health Agency of Canada website: http://www.phac-aspc.gc.ca/im/vpd-mev/varicella-eng.php

Duration of Effect

Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies are currently under evaluation in the follow up phase of studies. At the one year follow-up after a second dose of PRIORIX-TETRA (combined measles, mumps, rubella, varicella vaccine, live, attenuated), more than 98.8% of all children were seropositive for anti-measles, anti-rubella and anti-varicella antibodies, and 90.6% were seropositive for the anti-mumps antibodies.

STORAGE AND STABILITY

Store PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) at 2 to 8°C (in a refrigerator). Do not freeze. Store in the original packaging in order to protect from light.

The reconstituted vaccine should be administered as soon as possible. It may be kept up to 8 hours in the refrigerator (2 to 8°C).

The expiry date of the vaccine is indicated on the label and packaging.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) is supplied as a sterile powder (vial) and diluent (prefilled syringe* or ampoule) with or without needles.

**Format not available in Canada.*

Composition

After reconstitution, 1 dose (0.5 mL) contains:

Live, attenuated measles virus[1] (Schwarz strain)	not less than $10^{3.0}$ $CCID_{50}$[3]
Live, attenuated mumps virus[1] (RIT 4385 strain, derived from Jeryl Lynn strain)	not less than $10^{4.4}$ $CCID_{50}$[3]
Live, attenuated rubella virus[2] (Wistar RA 27/3 strain)	not less than $10^{3.0}$ $CCID_{50}$[3]
Live, attenuated varicella virus[2] (OKA strain)	not less than $10^{3.3}$ PFU

[1] produced in chick embryo cells
[2] produced in human diploid (MRC-5) cells
[3] Cell Culture Infective Dose 50%

Excipients: Amino acids, lactose, mannitol, sorbitol, water for injection.

Residue: neomycin sulphate.

Packaging

PRIORIX-TETRA is supplied as a lyophilized powder in a monodose vial in a pack size of 1*, 10, or 100*.

The diluent is available as 0.5 mL of solution in:

- An ampoule in pack sizes of 1*, 10 or 100*.
- A prefilled syringe with rubber stopper*. Pack sizes of 1 or 10 with 2 separate needles. Pack sizes of 1 or 10, without needles.

PRIORIX-TETRA and diluent are supplied in combination* as follows:

- 1 vial vaccine and 1 prefilled syringe of diluent with rubber stopper, with or without 2 needles. Pack size of 10.

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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: combined measles, mumps, rubella and varicella vaccine, live, attenuated

Product Characteristics

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) is a whitish to slightly pink coloured cake or powder contained in a glass vial sealed with a rubber stopper. The diluent (sterile water for injection) is clear and colourless. The reconstituted vaccine is a clear peach to fuchsia pink (bright pink) coloured solution.

CLINICAL TRIALS

Study demographics and trial design

PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live attenuated) has been evaluated in three pivotal clinical studies (038, 043 and 044).

Study 038 was a phase III study evaluating the consistency post dose 2 of three lots of PRIORIX-TETRA vaccine and non-inferiority of PRIORIX-TETRA vaccine compared to two doses of PRIORIX and one dose of VARILRIX, coadministered with PRIORIX at the first visit. The study continued for 3 years evaluating the persistence of antibodies of each of the vaccine antigens.

Study 043 was a phase III study evaluating the immunogenicity of lots near the end of the shelf life (aged) of PRIORIX-TETRA vaccine. A control group received two doses of PRIORIX and one dose of VARILRIX, coadministered with PRIORIX at the first visit.

Study 044 was a phase III study evaluating the consistency post dose 1 of three lots of PRIORIX-TETRA vaccine. Another study objective was to establish a seroconversion rate for mumps by neutralisation assay of at least 90% or higher. A control group received two doses of PRIORIX and one dose of VARILRIX, coadministered with PRIORIX at the first visit.

Study 046 was a phase II, open, randomized, comparative study to evaluate the immunogenicity and safety of PRIORIX-TETRA vaccine and PRIORIX, coadministered in separate injections with one dose of VARILRIX when given in healthy children who previously received a first dose of an MMR vaccine.

Study 047 was a phase II, open, randomized, comparative study to evaluate the immunogenicity and safety of PRIORIX-TETRA vaccine and PRIORIX, coadministered in separate injections with VARILRIX when given in healthy children who previously received a first dose of an MMR vaccine and one dose of a varicella vaccine.

Study 048 was a phase III study evaluating the immunogenicity and reactogenicity of PRIORIX-TETRA administered intramuscularly (IM), given according to a two-dose regimen (6 week interval), compared to subcutaneous (SC) administration.

For studies 038, 043 and 044, a total of 2206 healthy male and female subjects received at least one dose of PRIORIX-TETRA, of which 2173 vaccinees received the second dose of the vaccine 6 weeks after the first administration. The age at enrolment ranged from 9 through 23 months.

For studies 046 and 047, a total of 423 healthy male and female subjects received at least one dose of PRIORIX-TETRA, of which 153 were aged 24 months or less, and 270 were above 24 months of age. The age at enrolment ranged from 13 months through 6 years of age.

In study 048, an additional 328 healthy male and female subjects were given one dose of PRIORIX-TETRA at day 0, and given a second dose six weeks after the first administration, either via intramuscular or subcutaneous injection.

In studies 038, 043 and 044, baseline serum samples were obtained immediately prior to vaccine administration, at the time of the second injection and 6 weeks after. Anti-measles, anti-mumps and anti-rubella antibody titres were determined by an enzyme-linked immunosorbent assay (ELISA). Anti-mumps antibodies were also determined by neutralization test. Anti-varicella antibodies were determined by an indirect immunofluorescence assay (IFA).

Table 1 Summary of Demographic Characteristics (ATP cohort for Immunogenicity)

Study No.	Trial design	Dosage and route of administration	No. of subjects enrolled (total = 3770)	Mean age at administration in months (range)	Gender
038	Partially blinded, randomized, phase III, controlled, 2 doses, 4 parallel groups Study continued; ● 2 year follow up ● 3 year follow up	First dose on Day 0 and second dose on Day 42 by subcutaneous injection 2 doses of PRIORIX-TETRA or 2 doses of PRIORIX + 1 dose of VARILRIX	311 PRIORIX-TETRA 108 PRIORIX + VARILRIX	14.4 ± 2.30 (11 - 23) *23.5 ± 0.7 (21.0-25.0) **35.4 ± 0.7 (33.0-38.0)	PRIORIX-TETRA Male: 51.4% PRIORIX + VARILRIX Male: 52.8%
043	Partially blinded, randomized, phase III, controlled, 2 doses, 4 parallel groups	First dose on Day 0 and second dose on Day 42 by subcutaneous injection 2 doses of PRIORIX-TETRA or 2 doses of PRIORIX + 1 dose of VARILRIX	1162 PRIORIX-TETRA 193 PRIORIX + VARILRIX	14.0 ± 2.26 (11-21)	PRIORIX-TETRA Male: 51.5% PRIORIX + VARILRIX Male: 50. 3%
044	Partially blinded, randomized, phase III controlled, 2 doses, 4 parallel groups	First dose on Day 0 and second dose on Day 42 by subcutaneous injection 2 doses of PRIORIX-TETRA or 2 doses of PRIORIX + 1 dose of VARILRIX	681 PRIORIX-TETRA 219 PRIORIX + VARILRIX	12.9 ± 2.07 (11-20)	PRIORIX-TETRA Male: 51.4% PRIORIX + VARILRIX Male: 57.1%
046	Open, randomized, phase II, controlled, 2 parallel groups	First dose on Day 0 and second dose on Day 42-56 by subcutaneous injection First dose of PRIORIX-TETRA + 2nd dose of VARILRIX or First dose of PRIORIX and VARILRIX + 2nddose of VARILRIX	238 PRIORIX-TETRA VARILRIX 240 PRIORIX + VARILRIX. VARILRIX	31.7 ± 16.35 (15-83) 31.0 ± 15.68 (15-83)	PRIORIX-TETRA + VARILRIX Male 48.7% PRIORIX + VARILRIX. VARILRIX Male 51.8%

Study No.	Trial design	Dosage and route of administration	No. of subjects enrolled (total = 3770)	Mean age at administration in months (range)	Gender
047	Open, randomized, phase II, controlled, 2 parallel groups	First dose on Day 0 by subcutaneous injection 1 dose of PRIORIX-TETRA or 1 dose of PRIORIX + 1 dose of VARILRIX	195 PRIORIX-TETRA 195 PRIORIX + VARILRIX	47.4 ± 19.09 (15-75) 46.4 ± 19.09 (15-73)	PRIORIX-TETRA Male 49.7% PRIORIX + VARILRIX Male 45.5%
048	Open, randomized phase III, controlled, 2 doses, 2 parallel groups	First dose on Day 0 and second dose on Day 42 by subcutaneous injection	142 PRIORIX-TETRA (SC)	12.5 ± 2.0 (11-20)	PRIORIX-TETRA Male 57.7%
		First dose on Day 0 and second dose on Day 42 by intramuscular injection	141 PRIORIX-TETRA (IM)	12.6 ± 2.1 (11-20)	PRIORIX-TETRA Male 50.4%

*= Time between vaccination 2 and Year 2 (months)
**= Time between vaccination 2 and Year 3 (months)

Study results

Vaccine Immunogenicity

In studies 038, 043 and 044, a subset of 2,051 vaccinees who received at least one dose of PRIORIX-TETRA and 2,013 who received the second dose of vaccine were used in the immunogenicity analysis. The immunogenicity of PRIORIX-TETRA was similar to that of its individual component vaccines [PRIORIX (combined measles, mumps and rubella vaccine, live, attenuated) and VARILRIX (varicella virus vaccine, live, attenuated (OKA-strain))], which are commercially available and routinely used in immunization. (See Table 2)

Subjects in the PRIORIX-TETRA group received two doses of PRIORIX-TETRA given 6 weeks apart. Subjects in the PRIORIX+VARILRIX group received 1 dose of PRIORIX and 1 dose of VARILRIX as the first dose, and then 6 weeks later another dose of PRIORIX only.

Table 2 **Seroconversion rates observed in Study 038 following the first and second doses of PRIORIX-TETRA compared with PRIORIX and VARILRIX given separately**

Dose 1								
	PRIORIX-TETRA					PRIORIX + VARILRIX		
Antibody	**Lot**	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	A	106	97.2	92.0 to 99.4		106	100.0	96.6 to 100.0
	B*	100	99.0	94.6 to 100.0				
	C	100	97.0	91.5 to 99.4				
Mumps	A	105	91.4	84.4 to 96.0		106	95.3	89.3 to 98.5
	B*	98	85.7	77.2 to 92.0				
	C	99	92.9	86.0 to 97.1				
Rubella	A	106	97.2	92.0 to 99.4		106	100.0	96.6 to 100.0
	B*	100	100.0	96.4 to 100.0				
	C	100	100.0	96.4 to 100.0				
Varicella	A	105	99.0	94.8 to 100.0		106	100.0	96.6 to 100.0
	B*	99	100.0	96.3 to 100.0				
	C	100	100.0	96.4 to 100.0				
Dose 2								
	PRIORIX-TETRA					PRIORIX + VARILRIX		
Antibody	**Lot**	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	A	106	100.0	96.6 to 100.0		108	100.0	96.6 to 100.0
	B*	102	100.0	96.4 to 100.0				
	C	99	100.0	96.3 to 100.0				
Mumps	A	106	100.0	96.6 to 100.0		108	99.1	94.9 to 100.0
	B*	102	95.1	88.9 to 98.4				
	C	99	99.0	94.5 to 100.0				
Rubella	A	106	100.0	96.6 to 100.0		108	100.0	96.6 to 100.0
	B*	102	100.0	96.4 to 100.0				
	C	99	100.0	96.3 to 100.0				
Varicella	A	106	100.0	96.6 to 100.0		108	100.0	96.6 to 100.0
	B*	102	100.0	96.4 to 100.0				
	C	98	100.0	96.3 to 100.0				

Notes: Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows: Measles (ELISA): 150 mIU/mL, Mumps (ELISA): 231 U/mL, Mumps (Neutralizations): 1:28, Rubella (ELISA): 4 IU/mL, Varicella (IFA): 1:4

N = number of subjects in the specified group with available data

% = percentage of subjects who had seroconverted at a given timepoint

CI= confidence interval

Table 3 Seropositivity rates for antibodies observed in Study 038 after 2 and 3 years

2nd Year follow-up								
	PRIORIX-TETRA					**PRIORIX + VARILRIX**		
Antibody	**Lot**	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	A	82	100	95.6 to100.0		92	100	96.1 to 100.0
	B*	83	100	95.7 to 100.0				
	C	78	100	95.4 to 100.0				
Mumps	A	82	93.9	86.3 to 98.0		89	92.1	84.5 to 96.8
	B*	82	96.3	89.7 to 99.2				
	C	78	93.6	85.7 to 97.9				
Rubella	A	83	100	95.7 to 100.0		92	100	96.1 to 100.0
	B*	82	100	95.6 to 100.0				
	C	79	100	95.4 to 100.0				
Varicella	A	77	96.1	89.0 to 99.2		86	90.7	82.5 to 95.9
	B*	75	97.3	90.7 to 99.7				
	C	72	98.6	92.5 to 100.0				
3rd Year follow up								
	PRIORIX-TETRA					**PRIORIX + VARILRIX**		
Antibody	**Lot**	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	A	67	100	94.6 to 100.0		66	97.0	89.5 to 99.6
	B*	65	100	94.5 to 100.0				
	C	62	96.8	88.8 to 99.6				
Mumps	A	67	98.5	92.0 to 100.0		64	93.8	84.8 to 98.3
	B*	65	96.9	89.3 to 99.6				
	C	62	96.8	88.8 to 99.6				
Rubella	A	68	100	94.7 to 100.0		66	100	94.6 to 100.0
	B*	64	100	94.4 to 100.0				
	C	63	100	94.3 to 100.0				
Varicella	A	61	98.4	91.2 to 100.0		62	96.8	88.8 to 99.6
	B*	58	100	93.8 to 100.0				
	C	56	100	93.6 to 100.0				

Notes: Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows:
Measles (ELISA): 150 mIU/mL, Mumps (ELISA): 231 U/mL,
Rubella (ELISA): 4 IU/mL, Varicella (IFA): 1:4
N = number of subjects in the specified group with available data
% = percentage of subjects who had seroconverted at a given timepoint
CI= confidence interval
*B = experimental formulation

The Total Vaccinated Cohort years 2 and 3, include all vaccinated subjects in the summary study 038 who returned for the follow-ups. The results of the analysis were comparable in the group receiving PRIORIX-TETRA with those receiving PRIORIX + VARILRIX separately.

Table 4 Seroconversion rates observed in Study 043

Dose 1

	Lot D (aged)				Lot D (fresh)		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	372	97.0	94.8 to 98.5		387	97.4	95.3 to 98.8
Mumps (Neutra)	337	95.3	92.4 to 97.3		327	97.2	94.8 to 98.7
Mumps (ELISA)	360	88.9	85.2 to 91.9		378	91.3	88.0 to 93.9
Rubella	376	100	99.0 to 100		389	100	99.1 to 100
Varicella	358	97.2	94.9 to 98.7		374	98.9	97.3 to 99.7
	Lot E (aged)				**PRIORIX + VARILRIX**		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	384	97.9	95.9 to 99.1		190	95.3	91.2 to 97.8
Mumps (Neutra)	321	92.8	89.4 to 95.4		166	99.4	96.7 to 100
Mumps (ELISA)	371	88.1	84.4 to 91.2		182	95.1	90.8 to 97.7
Rubella	384	99.7	98.6 to 100		189	100	98.1 to 100
Varicella	373	96.8	94.4 to 98.3		184	95.7	91.6 to 98.1

Dose 2

	Lot D (aged)				Lot D (fresh)		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	365	99.2	97.6 to 99.8		380	99.7	98.5 to 100
Mumps (Neutra)	331	99.4	97.8 to 99.9		319	99.7	98.3 to 100
Mumps (ELISA)	366	99.2	97.6 to 99.8		379	98.4	96.6 to 99.4
Rubella	369	100	99.0 to 100		382	100	99.0 to 100
Varicella	351	100	99.0 to 100		367	99.7	98.5 to 100
	Lot E (aged)				**PRIORIX + VARILRIX**		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	380	99.2	97.7 to 99.8		188	98.4	95.4 to 99.7
Mumps (Neutra)	320	99.7	98.3 to 100		164	99.4	96.6 to 100
Mumps (ELISA)	376	97.6	95.5 to 98.9		185	99.5	97.0 to 100
Rubella	380	100	99.0 to 100		187	100	98.0 to 100
Varicella	371	100	99.0 to 100		182	97.3	93.7 to 99.1

Notes: Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows: Measles (ELISA): 150 mIU/mL, Mumps (ELISA): 231 U/mL, Mumps (Neutralizations): 1:28, Rubella (ELISA): 4 IU/mL, Varicella (IFA): 1:4

N = number of subjects in the specified group with available data

% = percentage of subjects who had seroconverted at a given timepoint

CI= confidence interval

Table 5 Seroconversion rates observed in Study 044

Dose 1							
	PRIORIX-TETRA				**PRIORIX + VARILRIX**		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	670	94.5	92.5 to 96.1		213	93.4	89.2 to 96.4
Mumps (Neutra)	558	96.1	94.1 to 97.5		187	93.6	89.1 to 96.6
Mumps (ELISA)	650	94.3	92.2 to 96.0		207	92.3	87.8 to 95.5
Rubella	667	99.7	98.9 to 100		212	98.1	95.2 to 99.5
Varicella	624	95.5	93.6 to 97.0		204	95.6	91.8 to 98.0
Dose 2							
	PRIORIX-TETRA				**PRIORIX**		
Antibody	**N**	**%**	**95% CI**		**N**	**%**	**95% CI**
Measles	657	98.3	97.0 to 99.2		209	97.6	94.5 to 99.2
Mumps (Neutra)	541	99.4	98.4 to 99.9		182	99.5	97.0 to 100
Mumps (ELISA)	656	99.2	98.2 to 99.8		208	99.5	97.4 to 100
Rubella	653	99.7	98.9 to 100		209	100	98.3 to 100
Varicella	615	99.7	98.8 to 100		199	97.5	94.2 to 99.2

Notes: Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows: Measles (ELISA): 150 mIU/mL, Mumps (ELISA): 231 U/mL, Mumps (Neutralizations): 1:28, Rubella (ELISA): 4 IU/mL, Varicella (IFA): 1:4

N = number of subjects in the specified group with available data

% = percentage of subjects who had seroconverted at a given timepoint

CI= confidence interval

Table 6 Pooled Analysis on Seroconversion Rates Post-Vaccination with PRIORIX-TETRA vs. PRIORIX + VARILRIX

Dose 1					
	PRIORIX-TETRA			**PRIORIX + VARILRIX**	
Antibody	**%**	**95% CI**		**%**	**95% CI**
Measles	**96.4**	95.5 to 97.2		**95.5**	93.3 to 97.1
Mumps (Neutra)	**95.4**	94.3 to 96.3		**96.8**	94.8 to 99.7
Mumps (ELISA)	**91.3**	90.0 to 92.5		**93.9**	91.5 to 95.9
Rubella	**99.7**	99.4 to 99.9		**99.2**	98.0 to 99.8
Varicella	**97.2**	96.3 to 97.9		**96.6**	94.5 to 98.0
Dose 2					
	PRIORIX-TETRA			**PRIORIX**	
Antibody	**%**	**95% CI**		**%**	**95% CI**
Measles	**99.1**	98.6 to 99.5		**98.4**	96.9 to 99.3
Mumps (Neutra)	**99.4**	98.9 to 99.7		**99.5**	98.4 to 99.9
Mumps (ELISA)	**98.8**	98.2 to 99.2		**99.4**	98.3 to 99.9
Rubella	**99.9**	99.6 to 100.0		**100.0**	99.3 to 100.0
Varicella*	**99.8**	99.5 to100.0		**98.0**	96.3 to 99.0

Notes: Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows: Measles (ELISA): 150 mIU/mL, Mumps (ELISA): 231 U/mL, Mumps (Neutralizations): 1:28, Rubella (ELISA): 4 IU/mL, Varicella (IFA): 1:4

% = percentage of subjects who had seroconverted at a given timepoint

CI= confidence interval

P value calculated using two-sided Wald test

* No significant differences ($p < 0.05$) were seen between groups for any antigen or for anytime point, with the exception of seroconversion to anti-varicella after the second dose.

Seroconversion rates elicited by subcutaneous dosing shows that after the first dose for subjects administered PRIORIX-TETRA ranged from 91.3% (for mumps by ELISA) to 99.7% (for rubella); values for the control group (PRIORIX + VARILRIX) ranged from 93.9% (for mumps by ELISA) to 99.2% (for rubella). Seroconversion rates post dose 2 were above 98% for all antigens in both groups.

At the one year follow-up after the second dose of PRIORIX-TETRA, no breakthrough cases were reported for measles, mumps and rubella despite reported contacts with wild virus. Exposures to varicella or zoster were reported in 14.2% in the PRIORIX-TETRA group versus 20.0% in the control group (PRIORIX + VARILRIX for the first dose; PRIORIX alone for the second dose). Breakthrough cases were reported in 0.34% of PRIORIX-TETRA recipients, as opposed to 1.9% of children in the control group. These data confirm that the vast majority of subjects who receive varicella vaccines and are exposed to wild-type virus are either completely protected from chickenpox or develop a milder form of the disease. These data also suggest a higher efficacy and a decrease in breakthrough varicella following two doses of vaccine as compared to one dose.

The absence of breakthrough cases of measles, mumps and rubella in the follow-up phase of the studies is supported by the experience with PRIORIX, for which only a low rate of vaccine failure has been observed. Further evidence of the effectiveness of the varicella component is provided by data on the impact of the use of VARILRIX on the incidence of varicella disease.

For studies 046 and 047, the immune response to PRIORIX-TETRA, MMR was assessed on 384 subjects from 13 months to 6 years of age, of whom 255 were more than two years old. PRIORIX-TETRA was administered as a second dose of MMR vaccine and as a first dose of varicella vaccine to the children in study 046. In study 047, PRIORIX-TETRA was administered as a second dose of MMR vaccine and as a second dose of varicella vaccine to the study children.

In children 25-72 months of age, the seropositivity rates were 100% for measles, mumps and rubella in both studies after PRIORIX-TETRA given as a second dose of MMR vaccine. The seropositive rates were 98.1% for varicella in study 046 after PRIORIX-TETRA given as a first dose of varicella vaccine and 100% for varicella in study 047 after PRIORIX-TETRA given as a second dose of varicella vaccine. The GMTs for all antigens 42 days post-vaccination were not reduced in children 25-72 months of age as compared to children 15-24 months of age in both studies. Table 7 presents the immunogenicity results by age group.

Overall, seropositivity rates to measles, mumps and rubella in children 25-72 months of age were within the same range as those observed in children 15-24 months of age within the same studies, and in previously reported studies. Therefore, these data indicate that the vaccine induces similar immune responses in children 2-6 years of age as compared to children 15-24 months of age. Taken together, these data support the indication of PRIORIX-TETRA, in children 2-6 years of age, in terms of the level of immune response induced.

Table 7 Antibody seropositivity rates observed in Study 046 and Study 047: 42-60 days post dose 1 of PRIORIX-TETRA in subjects less than or equal to 24 months of age and in subjects above 24 months of age

Study 046

Group	Timing	Measles		Mumps		Rubella		Varicella	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Toddlers	Pre	88	87.5 (78.7 to 93.6)	88	92.0 (84.3 to 96.7)	88	96.6 (90.4 to 99.3)	87	4.6 (1.3 to 11.4)
	PI (W6)	88	98.9 (93.8 to 100)	88	100 (95.9 to 100)	88	100 (95.9 to 100)	87	97.7 (91.9 to 99.7)
Children	Pre	107	95.3 (89.4 to 98.5)	107	92.5 (85.8 to 96.7)	107	99.1 (94.9 to 100)	107	11.2 (5.9 to 18.8)
	PI (W6)	107	100 (96.9 to 100)	107	100 (96.6 to 100)	107	100 (95.6 to 100)	107	98.1 (93.4 to 99.8)

Toddlers = subjects aged 15-24 months; Children= subjects aged 25-72 months
Pre = Day 0, PI (W6) = 6 weeks after the first vaccine dose
N = number of subjects, % percentage of subjects reporting a specified symptom, 95% CI= Exact 95% confidence interval

Study 047

Group	Timing	Measles		Mumps		Rubella		Varicella	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Toddlers	Pre	41	95.1 (83.5 to 99.4)	41	97.6 (87.1 to 99.9)	41	100 (91.4 to 100)	41	95.1 (83.5 to 99.4)
	PI (W6)	41	100 (91.4 to 100)	41	100 (91.4 to 100)	41	100 (91.4 to 100)	41	100 (91.4 to 100)
Children	Pre	148	96.6 (92.3 to 98.9)	148	97.3 (93.2 to 99.3)	148	100 (97.5 to 100)	145	96.6 (92.1 to 98.9)
	PI (W6)	148	100 (97.5 to 100)	148	100 (97.5 to 100)	148	100 (97.5 to 100)	145	100 (97.5 to 100)

Toddlers = subjects aged 15-24 months; Children= subjects aged 25-72 months
Pre = Day 0, PI (W6) = 6 weeks after the first vaccine dose
N = number of subjects, % percentage of subjects reporting a specified symptom, 95% CI= Exact 95% confidence interval

A comparative study (048) in 328 children who received PRIORIX-TETRA either by intramuscular or subcutaneous route (Table 8) demonstrated no significant differences between the two routes of administration, SC vs. IM, in terms of seroconversion rates for measles, mumps, rubella and varicella antibodies after the second dose for either administration routes.

Table 8 Seropositivity rates following vaccination with two doses of PRIORIX-TETRA (IM vs. SC)

Study 048

Group	Timing	Measles		Mumps		Rubella		Varicella	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
IM	Post (W12)	141	99.3 (96.1-100.0)	141	100.0 (97.4-100.0)	141	100.0 (97.4-100.0)	141	100.0 (97.4-100.0)
SC	Post (W12)	142	98.6 (95.0-99.8)	142	99.3 (96.1-100.0)	142	100.0 (97.4-100.0)	142	100.0 (97.4-100.0)

Seroconversion = titre ≥ cut-off in initially seronegative subjects. The cut-off of the tests is as follows: Measles (IFA): 150 mIU/mL, Mumps (IFA): 231 U/mL, Rubella (IFA): 4 IU/mL, Varicella (IFA): 1:4
N = the total number of subjects with results available - i.e. subjects with a seronegative, a seropositive or unknown pre-vaccination status
95% CI = 95% confidence interval
POST (W12) = post-vaccination time point at Week 12

Vaccine Safety

In the clinical studies, the safety profile presented below is mainly derived from the pivotal clinical studies 038, 043, and 044. Table 9 summarizes the reactogenicity profile of PRIORIX-TETRA post doses 1 and 2 in terms of solicited local (pain, redness, swelling) and general symptoms (fever and rash) for each study separately.

Table 9 Incidence of General Symptoms Reported Post-Vaccination with PRIORIX-TETRA vs. PRIORIX + VARILRIX

Study No.	Dose No.	Dosage	Symptoms in % population					
			Redness at injection site	**Pain**	**Swelling**	**Fever ≥ 38°C**	**Fever > 39.5°C**	**Rash**
			Day 0-3 post vaccination	Day 0-3 post vaccination	Day 0-3 post vaccination	Day 0-14 post vaccination	Day 0-14 post vaccination	Day 0-43 post vaccination
038	1	PRIORIX-TETRA	30.5	12.1	10.0	67.7	11.6	16.4
		PRIORIX +	23.6	5.7	8.1	48.8	10.6	13.0
		VARILRIX	20.5	6.6	9.8			
	2	PRIORIX-TETRA	33.8	14.6	14.3	43.1	6.0	6.0
		PRIORIX	22.1	4.1	9.0	47.5	5.7	5.7
043*	1	PRIORIX-TETRA	23.3 to 24.1	8.3 to 11.3	7.6 to 7.8	59.1 to 61.7	10.0 to 12.9	18.9 to 21.5
		PRIORIX +	21.6	8.5	4.7	38.0	4.2	19.7
		VARILRIX	18.9	9.0	5.7			
	2	PRIORIX-TETRA	28.5 to 32.0	9.4 to 10.5	10.9 to 13.3	20.9 to 22.8	0.8 to 3.7	11.2 to 12.8
		PRIORIX	12.6	2.4	2.4	20.8	1.4	7.7
044	1	PRIORIX-TETRA	31.7	8.5	10.4	59.8	10.7	20.1
		PRIORIX +	29.7	6.5	6.5	51.3	8.8	13.9
		VARILRIX	29.9	7.3	7.3			
	2	PRIORIX-TETRA	32.3	9.5	13.2	36.8	3.6	12.7
		PRIORIX	24.7	6.8	8.5	33.1	4.7	15.3

*The results from study 043 are presented as a range since the analysis was done per lot of PRIORIX-TETRA used in the study.

Table 10 Pooled Analysis on Safety in Studies 038, 043 and 044

Dose 1						
	PRIORIX-TETRA N = 2206			**PRIORIX + VARILRIX N = 574**		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Pain (Day 0-3)	209	9.47	8.28 to 10.77	50	8.71	6.53 to 11.32
Redness (Day 0-3)	596	27.02	25.17 to 28.92	157	27.35	23.74 to 31.20
Swelling (Day 0-3)	186	8.43	7.31 to 9.67	46	8.01	5.93 to 10.54
Fever ≥ 38.0°C (Day 0-14)	1349	61.15	59.08 to 63.19	263	45.82	41.69 to 49.99
Fever > 39.5°C (Day 0-14)	247	11.20	9.91 to 12.59	43	7.49	5.47 to 9.96
Rash (0-42)	448	20.31	18.65 to 22.05	94	16.38	13.44 to 19.66
Dose 2						
	PRIORIX-TETRA N = 2173			**PRIORIX N = 565**		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Pain (Day 0-3)	222	10.22	8.97 to 11.57	26	4.60	3.03 to 6.67
Redness (Day 0-3)	674	31.02	29.08 to 33.01	111	19.65	16.45 to 23.17
Swelling (Day 0-3)	267	12.29	10.94 to 13.74	36	6.37	4.50 to 8.71
Fever ≥ 38.0°C (Day 0-14)	636	29.27	27.36 to 31.23	179	3.68	27.86 to 35.69
Fever > 39.5°C (Day 0-14)	68	3.13	2.44 to 3.95	21	3.72	2.32 to 5.63
Rash (0-42)	249	11.46	10.15 to 12.87	59	10.44	8.04 to 13.26

N = number of subject having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom
95% CI = Exact 95% confidence interval

The pooled analysis of studies 038, 043 and 044, given subcutaneously, showed no differences in redness, pain and swelling experienced by the children in the two groups (PRIORIX-TETRA and PRIORIX + VARILRIX) after their first dose. The children who received PRIORIX-TETRA as their second dose experienced more of these symptoms when compared to those received PRIORIX. No statistically significant differences were observed between the vaccine groups for either the first or the second dose for rash.

After the first dose, the observed incidence of fever during the follow up period was higher in the PRIORIX-TETRA group as compared to the PRIORIX + VARILRIX group. No differences in fever were observed between the two vaccine groups after the second dose.

The incidences of adverse events in studies 046 and 047, which included children ≥ 24 months, were within the range of value's reported in studies 038, 043 and 044.

In study 048, the results showed that there was no difference between the IM group vs. SC group with regards to the local and general solicited symptoms of the vaccine and were within the range of values reported for previous studies.

Administration of PRIORIX-TETRA with other vaccines

Clinical studies have demonstrated that PRIORIX-TETRA (combined measles, mumps, rubella and varicella vaccine, live, attenuated) can be given simultaneously with any of the following monovalent or combination vaccines: hexavalent vaccines (DTaP-HBV-IPV-Hib), diphtheria-tetanus-acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type b vaccine (Hib), inactivated polio vaccine (IPV), Hepatitis B vaccine (HBV), meningococcal serogroup B vaccine (MenB - BEXSERO), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (MenACWY) and 10-valent pneumococcal conjugate vaccine (PCV).

In Study 013, children who had previously received a complete primary vaccination course against diphtheria, tetanus, pertussis, hepatitis B, polio and *Haemophilus influenzae* type b received INFANRIX HEXA as a booster dose, co-administered with PRIORIX-TETRA. Control groups received either PRIORIX-TETRA or INFANRIX HEXA alone. Based on the results, there was no evidence of any clinically relevant interference with the immune response to the measles, mumps, rubella and varicella antigens following co-administration with INFANRIX HEXA.

Study MenACWY-TT-039 demonstrated non-inferiority of the seroconversion rates for anti-measles, mumps, rubella, and varicella zoster virus (VZV) antibodies 42 days after the first dose of PRIORIX-TETRA when administered concomitantly with meningococcal group A, C, W-135 and Y conjugate vaccine (MenACWY-TT - Nimenrix) versus separately at different visits.

Study V72P13E1 assessed the concomitant use of PRIORIX-TETRA and BEXSERO, and demonstrated non-inferiority of seroconversion (≥ 1.25 gpELISA units/mL), but not of seroprotection (≥ 5 gpELISA units/mL) for varicella after the first dose. The difference between the groups was 2% (95% CI, -11%, 7%). The clinical implication of these differences remains unknown.

Study MMRV-063 demonstrated the non-inferiority of PRIORIX-TETRA co-administered with MenC conjugate vaccine (Meningitec) compared to the first dose of PRIORIX-TETRA alone with respect to anti-measles, anti-mumps, anti-rubella and anti-varicella seroconversion rates at Day 42 after Dose 1.

Study 10PN-PD-DIT-022 assessed the immunogenicity of PRIORIX-TETRA and 10-valent pneumococcal conjugate vaccine (SYNFLORIX) when co-administered with each other. Study 10PN-PD-DIT-022 confirmed that the immunogenicity of PRIORIX-TETRA is not compromised when co-administered with 10-valent pneumococcal conjugate vaccine.

TOXICOLOGY

A repeated dose toxicity study in animals did not reveal any local or systemic toxicity of the vaccine.

REFERENCES

1. Centers for Disease Control. Measles, Mumps, and Rubella - Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congential Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1998;Vol.47 (No. RR-8) 1-58.

2. Dennehy PH, Reisinger KS, Blatter MM, Veloudis BA. Immunogenicity of subcutaneous versus intramuscular OKA/Merck varicella vaccination in healthy children. Pediatrics. 1991: 88(3):604-607.

3. Health Canada. Proceedings of the 4th Canadian National Immunization Conference. Immunization in the 21th Century: Progress Through Education; 2000 Dec 3-6; Halifax, Canada. Canada Communicable Disease Report (CCDR); 2001; 27S5: 1-39.

4. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006 1;55(RR- 15):1-48.

5. National Advisory Committee on Immunization: Canadian Immunization Guide, Sixth Edition. Minister of Public Works and Government Services Canada, 2002.

6. Peltola H and Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. Lancet. 1986;1(8487):939-42.

7. Public Health Agency of Canada (PHAC). Update on the Elimination of Measles in Canada, 1998. Canada Communicable Disease Report (CCDR); 1999; 25-05 [cited 2006 May 18, about 6 pages]. Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/99vol25/dr2505eb.html

8. Strebel PM, Papania MJ, Halsey NA. Measles vaccine. In: Plotkin S, Orenstein W, editors. Vaccines. 4th ed. Philadelphia: Saunders; 2004. p. 389-440

PART III: CONSUMER INFORMATION

PRIORIX-TETRA

Combined measles, mumps, rubella and varicella vaccine, live, attenuated

This leaflet is part III of a three-part "Product Monograph" published when PRIORIX-TETRA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PRIORIX-TETRA. Contact your doctor or pharmacist if you have any questions about the vaccine.

Keep this leaflet. You may need to read it again.

ABOUT THIS VACCINE

What the vaccine is used for:
PRIORIX-TETRA is a vaccine used in children from the age of 9 months up to 6 years of age for protection against measles, mumps, rubella and chicken pox (varicella) diseases.

PRIORIX-TETRA may be used in individuals up to 12 years of age based upon previous experience with the separate component vaccines, PRIORIX (combined measles, mumps and rubella vaccine, live, attenuated) and VARILRIX [varicella virus vaccine, live, attenuated (OKA-strain)].

- **Measles:** Measles is an infectious illness caused by a virus. It is passed on by breathing in droplets in the air from infected people. The main signs of the illness include a rash, runny nose and a fever. Some people can get other symptoms that include ear infections, chest infections such as bronchitis and pneumonia, and fits. Measles can be fatal. These effects are more common in underfed or ill children.

- **Mumps**: Mumps is an infectious illness also caused by a virus. It is passed on by breathing in droplets in the air from infected people. The main sign of the illness is swelling of the glands near the ears, on one or both sides of the face in the cheek area. Some people also have inflammation of the pancreas, inflammation of the ovaries or testicles that sometimes cause fertility problems in later life, meningitis, and deafness that continues after recovering from the illness itself.

- **Rubella**: Rubella is an infectious illness also caused by a virus. The main signs of rubella are a rash and swollen glands. If pregnant women get rubella infection in the first 12 weeks of pregnancy it can cause damage to the unborn child in about nine out of 10 cases. This damage can include mental handicap, blindness, deafness and heart problems.

- **Varicella**: Chickenpox (varicella) is an infectious illness caused by a virus called varicella zoster. It is passed on by close contact with infected people and by breathing in droplets in the air from infected people. It is most common in children under the age of 10 in whom it is usually mild. The main sign of the illness is a rash with raised red spots on the face and head which may spread to other parts of the body. Chickenpox can be more serious in adults, in pregnant women and patients who have a poor immune system.

What it does:
PRIORIX-TETRA contains a live, weakened form of the measles, mumps, rubella and varicella viruses. When a person is given the vaccine, the immune system (the body's natural defence system) will make antibodies against these viruses. These antibodies protect against measles, mumps, rubella and varicella infections.

The weakened viruses that are in PRIORIX-TETRA are rarely passed on from the person who has had the vaccine to other people. This can happen with the varicella virus only when the healthy person has developed blisters.

As with all vaccines, PRIORIX-TETRA may not completely protect all people who are vaccinated.

When it should not be used:
Do not use PRIORIX-TETRA if your child:

- Has previously experienced an allergic reaction to PRIORIX-TETRA, neomycin (an antibiotic) or any component contained in this vaccine (see What the medicinal ingredient is and What the important nonmedicinal ingredients are sections). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. However, if you had a skin rash (dermatitis) after treatment with neomycin, you can still be vaccinated with PRIORIX-TETRA.

- Has previously experienced an allergic reaction to any vaccine against measles, mumps, rubella and varicella diseases.

- Has any severe illness or takes any medicine that weakens the immune system.

PRIORIX-TETRA must not be given during pregnancy. Pregnancy should be avoided for one month after vaccination. During this time your daughter should use an effective method of birth control to avoid pregnancy. If your daughter is pregnant or breast-feeding, think she may be pregnant or is planning to have a baby, ask your doctor or pharmacist before the vaccine is given.

What the medicinal ingredient is:
Each 0.5 mL dose of PRIORIX-TETRA contains not less than $10^{3.0}$ $CCID_{50}$ of the Schwarz measles, not less than $10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps, not less than $10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella and not less than $10^{3.3}$ PFU OKA varicella virus strains.

What the important nonmedicinal ingredients are:
PRIORIX-TETRA contains the following nonmedicinal ingredients: amino acids, lactose, mannitol, sorbitol, and water for injection. Residue: neomycin sulphate.

What dosage forms it comes in:
PRIORIX-TETRA is supplied as a whitish powder in a single dose glass vial with either a glass ampoule or a pre-filled syringe* of clear colourless sterile liquid (diluent) for reconstituting the vaccine.
**Format not available in Canada.*

When the vaccine is reconstituted it may vary from clear peach to fuchsia pink (bright pink).

WARNINGS AND PRECAUTIONS

BEFORE you use PRIORIX-TETRA talk to your doctor or pharmacist if your child:

- Has a severe infection with a high temperature. In these cases, the vaccination will be postponed until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- Has a history of febrile convulsions (fits) or a family history of convulsions. In this case your child should be closely monitored after vaccination as fever may occur 5 to 12 days after vaccination.
- Has had previous allergic reactions, impaired defense against infection or is pregnant.
- Has a history or a family history of allergies.
- Has ever had a severe allergic reaction to eggs or anything that contained eggs.
- Has had a side effect after vaccination against measles, mumps or rubella that involved easy bruising or bleeding for longer than usual.
- Has had a blood or plasma transfusion, or human immunoglobulin within the last three months. If so, the antibody response to PRIORIX-TETRA may be low so it is usual to wait for three months before giving PRIORIX-TETRA.
- Is due to have a skin test for possible tuberculosis. If this test is done within 6 weeks after receiving PRIORIX-TETRA, the result may not be reliable.
- Has a weakened immune system. Your child should be closely monitored as the responses to the vaccines may not be sufficient to ensure a protection against the illness.

As with other vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic events (severe allergic reaction that can be life threatening) following the administration of the vaccine.

Like other vaccines, PRIORIX-TETRA cannot completely protect your child against catching chickenpox. However, people who have been vaccinated and catch chickenpox usually have a very mild disease, compared with people who have not been vaccinated.

Fainting can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if you or your child fainted with a previous injection.

INTERACTIONS WITH THIS VACCINE

Tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Aspirin or Aspirin-type products (also known as salicylates) should not be taken for 6 weeks after vaccination, since we now know that Reye's Syndrome, a rare disease of the brain and liver, could occur.

PRIORIX-TETRA can be given at the same time as other vaccines. A different injection site will be used for each vaccine.

PROPER USE OF THIS VACCINE

Usual dose:
Your child will receive two doses of PRIORIX-TETRA. Your doctor will advise you when to take the second dose.

PRIORIX-TETRA will be given as an injection under the skin or into the muscle. Your doctor may wipe the skin with alcohol or other disinfecting agents and will let the skin dry before the injection.

Missed Dose:
Make sure your child finishes the complete vaccination course. If not, your child may not be fully protected against infection.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The safety of measles-mumps-rubella and varicella vaccines has been well characterised in clinical trials and post-marketing surveillance. PRIORIX (combined measles, mumps and rubella vaccine, live, attenuated) and VARILRIX [varicella virus vaccine, live, attenuated (OKA-strain)], have been used in Canadian market since 2002 and 2003 respectively. Over 144 million doses of PRIORIX and 14 million doses of VARILRIX have been distributed worldwide since 1997 and 1994 respectively. No safety concerns outside the recognized and reported safety profile has been identified to date.

Like other vaccines, PRIORIX-TETRA may occasionally cause unwanted effects, although not everybody gets them.

As with all injectable vaccines, there is an extremely small risk of allergic reactions. These may be local or widespread rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's office. However, you should seek immediate treatment in any event.

Side effects that occurred during clinical trials with PRIORIX-TETRA were as follows:

- Very common (these may occur with more than 1 in 10 doses of the vaccine):
  - local pain
  - local redness
  - fever greater than 37.5°C*
- Common (these may occur with up to 1 in 10 doses of the vaccine):
  - local swelling
  - fever greater than 39°C*
  - irritability
  - rash (spots and/or blisters)
- Uncommon (these may occur with up to 1 in 100 doses of the vaccine):
  - upper respiratory tract infection
  - crying
  - generally feeling unwell
  - swollen glands in the cheek
  - diarrhea
  - vomiting
  - loss of appetite
  - inability to sleep
  - fatigue
  - lack of energy
  - nervousness
  - runny nose
  - swollen glands in the neck, armpit and groin
- Rare (these may occur with up to 1 in 1,000 doses of the vaccine):
  - bronchitis
  - infection of the middle ear
  - coughing
  - seizures with fever

After commercialization the following additional side effects have been reported rarely in people vaccinated with PRIORIX-TETRA:

- infection around the brain or spinal cord (meningitis)
- shingles (herpes zoster)
- measles-like symptoms
- mumps-like symptoms (including transient, painful swelling of the testicles and swollen glands in the neck)
- infection or inflammation of the brain, spinal cord and peripheral nerves resulting in temporary difficulty when walking (unsteadiness) and/or temporary loss of control of bodily movements), stroke, inflammation of some nerves, possibly with tingling or numbness, or loss of normal movement (Guillain Barré syndrome)
- narrowing or blockage of blood vessels. This may include unusual bleeding or bruising under the skin (Henoch Schonlein purpura) or fever which lasts for more than five days, associated with a rash on the trunk sometimes followed by a peeling of the skin on the hands and fingers, red eyes, lips, throat and tongue (Kawasaki disease)
- bleeding or bruising more easily than normal due to a drop in a type of blood cell called platelets, unusual bleeding or bruising under the skin
- severe condition of the skin that may affect the mouth and other parts of the body
- chickenpox-like rash
- joint and muscle pains

* Higher rates of fever were observed after administration of the first dose of PRIORIX-TETRA when compared to PRIORIX and VARILRIX vaccines administered separately at the same visit.

This is not a complete list of side effects. For any unexpected effects while taking PRIORIX-TETRA*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store PRIORIX-TETRA in a refrigerator (2 to 8°C) and in the original package in order to protect from light.

Do not freeze.

Keep out of the reach and sight of children.

Do not use PRIORIX-TETRA after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca
At the following website:
http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
Address Locator 6502A
K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.gsk.ca
or by contacting the sponsor,
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7333 Mississauga Road
Mississauga, Ontario
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