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Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Menactra®

FOR INTRAMUSCULAR INJECTION

℞ only

6122

INDICATIONS AND USAGE
Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age.

Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroup B.

DOSAGE AND ADMINISTRATION
Menactra vaccine should be administered as a single 0.5 mL injection by the intramuscular route, preferably in the anterolateral thigh or deltoid region depending on the recipient's age and muscle mass.

In children 9 through 23 months of age, Menactra is given as a 2-dose series at least three months apart.

Individuals 2 through 55 years of age receive a single dose.

Do not administer this product intravenously, subcutaneously, or intradermally.

The need for, or timing of, a booster dose of Menactra vaccine has not yet been determined.

Parenteral drug products should be inspected visually for container integrity, particulate matter, and discoloration prior to administration, whenever solution and container permit.

CONTRAINDICATIONS
Hypersensitivity
Severe allergic reaction (eg, anaphylaxis) after a previous dose of a meningococcal capsular polysaccharide-, diphtheria toxoid- or CRM_{197}-containing vaccine, or to any component of Menactra vaccine (see **DESCRIPTION**).

Guillain-Barré Syndrome
Known history of Guillain-Barré syndrome (GBS) is a contraindication to vaccine administration (see **WARNINGS AND PRECAUTIONS**).

Febrile or Acute Disease
Vaccination must be postponed in case of febrile or acute disease. However, a minor febrile or non-febrile illness, such as mild upper respiratory infection, is not usually a reason to postpone immunization.

Pregnancy
Refer to section on **Pregnancy**.

WARNINGS AND PRECAUTIONS
Guillain-Barré Syndrome
GBS has been reported in temporal relationship following administration of Menactra vaccine (see **Post-Marketing Reports**). An early evaluation of post-marketing adverse events suggested a potential for an increased risk of GBS following Menactra vaccination. However, a recent multi-site retrospective cohort and nested case-control study involving over 12 million adolescents, of whom 1.4 million received Menactra vaccine, found no evidence of increased GBS risk associated with the use of Menactra vaccine. Nonetheless, persons previously diagnosed with GBS should not receive Menactra vaccine (see **CONTRAINDICATIONS**).

Preventing and Managing Allergic Vaccine Reactions
Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

Thrombocytopenia or Bleeding Disorders
Menactra vaccine has not been evaluated in persons with thrombocytopenia or bleeding disorders. As with any other vaccine administered intramuscularly, the vaccine risk versus benefit for persons at risk of hemorrhage following intramuscular injection must be evaluated.

Altered Immunocompetence
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to Menactra vaccine.

Limitations of Vaccine Effectiveness
Menactra vaccine may not protect all recipients against vaccine serogroups.

ADVERSE REACTIONS
Clinical Trial Adverse Reactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Children 9 Through 23 Months of Age
The safety of Menactra vaccine was evaluated in four clinical studies that enrolled 3721 participants who received Menactra vaccine at 9 and 12 months of age. At 12 months of age, these children also received one or more other vaccines [Measles, Mumps, Rubella and Varicella Virus Vaccine Live (MMRV) or Measles, Mumps, and Rubella Virus Vaccine (MMR) and Varicella Virus Vaccine Live (V); Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (PCV7); Hepatitis A Vaccine (HepA)]. A control group of 997 children was enrolled at 12 months of age and received two or more childhood vaccines [MMRV (or MMR + V), PCV7, HepA] at 12 months of age (see **CLINICAL STUDIES - Concomitant Vaccine Administration**). Three percent of individuals received MMR and V, instead of MMRV, at 12 months of age.

The primary safety study was a controlled trial that enrolled 1256 children who received Menactra vaccine at 9 and 12 months of age. At 12 months of age, these children received MMRV (or MMR + V), PCV7, and HepA. A control group of 522 children received MMRV, PCV7, and HepA. Of the 1778 children, 78% of participants (Menactra vaccine, N=1056; control group, N=322) were enrolled at United States (US) sites and 22% at a Chilean site (Menactra vaccine, N=200; control group, N=200).

Individuals 2 Through 55 Years of Age

The safety of Menactra vaccine was evaluated in eight clinical studies that enrolled 10,057 participants aged 2–55 years who received Menactra vaccine and 5266 participants who received Menomune – A/C/Y/W-135 vaccine. The three primary safety studies were randomized, active-controlled trials that enrolled participants 2–10 years of age (Menactra vaccine, N=1713; Menomune – A/C/Y/W-135 vaccine, N=1519), 11–18 years of age (Menactra vaccine, N=2270; Menomune – A/C/Y/W-135 vaccine, N=972), and 18–55 years of age (Menactra vaccine, N=1384; Menomune – A/C/Y/W-135 vaccine, N=1170), respectively.

Serious Adverse Events in All Safety Studies

Serious adverse events (SAEs) were reported during a 6-month time period following vaccinations in individuals 9 months through 55 years of age. In children who received Menactra vaccine at 9 months and at 12 months of age, SAEs occurred at a rate of 2.0% - 2.5%. In participants who received one or more childhood vaccine(s) (without co-administration of Menactra vaccine) at 12 months of age, SAEs occurred at a rate of 1.6% - 3.6%, depending on the number and type of vaccines received. In children 2–10 years of age, SAEs occurred at a rate of 0.6% following Menactra vaccine and at a rate of 0.7% following Menomune – A/C/Y/W-135 vaccine. In adolescents 11 through 18 years of age and adults 18 through 55 years of age, SAEs occurred at a rate of 1.0% following Menactra vaccine and at a rate of 1.3% following Menomune – A/C/Y/W-135 vaccine.

Solicited Adverse Events in the Primary Safety Studies

The most frequently reported solicited injection site and systemic adverse reactions within 7 days following vaccination in children 9 months and 12 months of age were injection site tenderness and irritability.

The most frequently reported solicited local and systemic adverse reactions in children aged 2–10 years were injection site pain, irritability, diarrhea, drowsiness, and anorexia. In adolescents ages 11–18 years and adults ages 18–55 years, the most commonly reported reactions were injection site pain, headache, and fatigue. Except for redness in adults, injection site reactions were more frequently reported after Menactra vaccination than after Menomune – A/C/Y/W-135 vaccination.

Adverse Events in Concomitant Vaccine Studies

Solicited Injection Site and Systemic Reactions When Given With Other Pediatric Vaccines

In the primary safety study, 1378 US children were enrolled to receive Menactra vaccine alone at 9 months of age and Menactra vaccine plus one or more other routinely administered vaccines (MMRV, PCV7, and HepA) at 12 months of age (N=961). Another group of children received two or more administered vaccines (MMRV, PCV7, and HepA vaccines) (control group, N=321) at 12 months of age. Participants who received Menactra vaccine and the concomitant vaccines at 12 months of age described above reported similar frequencies of tenderness, redness, and swelling at the Menactra vaccine injection site and at the concomitant vaccine injection sites. Tenderness was the most frequent injection site reaction (48%, 39%, 46%, and 43% at the Menactra vaccine, MMRV, PCV7, and HepA vaccine sites, respectively). Irritability was the most frequent systemic reaction, reported in 62% of recipients of Menactra vaccine plus concomitant vaccines, and 65% of control group. (See **CLINICAL STUDIES - Concomitant Vaccine Administration**).

Solicited Injection Site and Systemic Reactions When Given With Tetanus and Diphtheria Toxoid Adsorbed Vaccine (Td)

Injection site pain was reported more frequently after Td vaccination than after Menactra vaccination (71% versus 53%). The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra vaccine was administered 28 days after Td (59% versus 36%). In both groups, the most common reactions were headache (Menactra vaccine + Td, 36%; Td + Placebo, 34%; Menactra vaccine alone, 22%) and fatigue (Menactra vaccine + Td, 32%; Td + Placebo, 29%; Menactra vaccine alone, 17%). Fever ≥40.0°C occurred at ≤0.5% in all groups.

Solicited Injection Site and Systemic Reactions When Given With Typhoid Vi Polysaccharide Vaccine

More participants experienced pain after Typhoid vaccination than after Menactra vaccination (Typhoid + Placebo, 76% versus Menactra vaccine + Typhoid, 47%). The majority (70%-77%) of injection site solicited reactions for both groups at either injection site were reported as Grade 1 and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra vaccine + Typhoid, 41%; Typhoid + Placebo, 42%; Menactra vaccine alone, 33%) and fatigue (Menactra vaccine + Typhoid, 38%; Typhoid + Placebo, 35%; Menactra vaccine alone, 27%). Fever ≥40.0°C and seizures were not reported in either group.

Post-Marketing Reports

In addition to reports in clinical trials, worldwide voluntary adverse events reports received since market introduction of Menactra vaccine are listed below. Because these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to Menactra vaccine exposure.

Immune system disorders - Hypersensitivity reactions such as anaphylaxis/anaphylactic reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

Nervous system disorders - Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis

Musculoskeletal and connective tissue disorders - Myalgia

DRUG INTERACTIONS

Concomitant Administration with Other Vaccines

Menactra vaccine was concomitantly administered with Typhim Vi® [Typhoid Vi Polysaccharide Vaccine] (Typhoid) and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td), in individuals 18 through 55 and 11 through 17 years of age, respectively. In children younger than 2 years of age, Menactra was co-administered with one or more of the following vaccines: PCV7, MMR, V, MMRV, HepA, or Hib vaccine (see **CLINICAL STUDIES** and **ADVERSE REACTIONS**).

Pneumococcal antibody responses to some serotypes in PCV7 were decreased following co-administration of Menactra vaccine and PCV7. Given the high antibody response rates when assessed by either ELISA or OPA, it is unlikely that there will be any impact on the clinical efficacy of either of these vaccines when administered concomitantly (see **CLINICAL STUDIES - Concomitant Vaccine Administration**).

Do not mix Menactra vaccine with other vaccines in the same syringe. When Menactra vaccine is administered concomitantly with other injectable vaccines, the vaccines should be administered with different syringes and given at separate injection sites.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

USE IN SPECIFIC POPULATIONS

Pregnancy

Animal reproduction studies have not demonstrated a risk with respect to effects on pregnancy and embryo-fetal development, parturition, and postnatal development. However, since there are no data on the use of this vaccine in pregnant women, Menactra vaccine should be given to a pregnant woman only if clearly needed, such as during an outbreak or prior to necessary travel to an endemic area, and only following an assessment involving the healthcare professional and patient of the risks and benefits.

Considering the severity of the meningococcal disease, pregnancy should not preclude vaccination when the risk is clearly identified.

Nursing Mothers

It is not known whether Menactra vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Menactra vaccine is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Menactra vaccine in infants below 9 months of age have not been established.

Geriatric Use

Safety and effectiveness of Menactra vaccine in adults older than 55 years have not been established.

DESCRIPTION

Menactra is a sterile, intramuscularly administered vaccine that contains *N meningitidis* serogroup A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. *N meningitidis* A, C, Y and W-135 strains are cultured on Mueller Hinton agar and grown in Watson Scherp media. The polysaccharides are extracted from the *N meningitidis* cells and purified by centrifugation, detergent precipitation, alcohol precipitation, solvent extraction and diafiltration. To prepare the polysaccharides for conjugation, they are depolymerized, derivatized, and purified by diafiltration. *Corynebacterium diphtheriae* cultures are grown in a modified Mueller and Miller medium and detoxified with formaldehyde. The diphtheria toxoid protein is purified by ammonium sulfate fractionation and diafiltration. The derivatized polysaccharides are covalently linked to diphtheria toxoid and purified by serial diafiltration. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during manufacture. Each 0.5 mL dose may contain residual amounts of formaldehyde of less than 2.66 mcg (0.000532%), by calculation. Potency of Menactra vaccine is determined by quantifying the amount of each polysaccharide antigen that is conjugated to diphtheria toxoid protein and the amount of unconjugated polysaccharide present.

Menactra vaccine is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier.

There is no latex in any component of the vial.

CLINICAL PHARMACOLOGY

Mechanism of Action

The presence of bactericidal anti-capular meningococcal antibodies has been associated with protection from invasive meningococcal disease. Menactra vaccine induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Menactra vaccine has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

CLINICAL STUDIES

Efficacy

The Serum Bactericidal Assay (SBA) used to test sera contained an exogenous complement source that was either human (SBA-H) or baby rabbit (SBA-BR).

The response to Menactra vaccination administered to children 9 months through 10 years of age was evaluated by the proportion of subjects having an SBA-H antibody titer of 1:8 or greater, for each serogroup. In individuals 11 through 55 years of age, the response to Menactra vaccination was evaluated by the proportion of subjects with a 4-fold or greater increase in baseline bactericidal antibody to each serogroup as measured by SBA-BR. For individuals 2 through 55 years of age, vaccine efficacy was inferred from the demonstration of immunologic equivalence to a US-licensed meningococcal polysaccharide vaccine, Menomune – A/C/Y/W-135 vaccine as assessed by Serum Bactericidal Assay (SBA).

Immunogenicity

Children 9 through 23 Months of Age

In a randomized, US, multi-center trial, children received Menactra vaccine at 9 months and 12 months of age. The first Menactra vaccine dose was administered alone, followed by a second Menactra vaccine dose given alone (N=404), or with MMRV vaccine (N=302), or with PCV7 (N=422). For all participants, sera were obtained approximately 30 days after last vaccination. There were no substantive differences in demographic characteristics between the vaccine groups. The median age range for administration of the first dose of Menactra vaccine was at approximately 9 months of age.

Administration of 2 doses of Menactra vaccine to children at 9 months through 15 months of age was evaluated in US studies. In the primary immunogenicity study, children received Menactra vaccine at 9 and 12 months of age, the majority of the participants in groups that received the second dose of Menactra vaccine alone or with concomitant pediatric vaccine(s), achieved SBA-HC titers ≥1:8 for all serogroups. Groups that received the second dose of Menactra vaccine alone had ≥91% of subjects achieving an SBA-HC titer ≥1:8 for serogroups A, C, and Y and ≥86% for serogroup W-135. When the second dose of Menactra vaccine was given concomitantly with MMRV (or MMRV + Hib) or with PCV, the percentages of subjects with SBA-HC titers ≥1:8 were high (>90% for serogroups A, C, and Y and >81% for serogroup W-135). SBA-HC GMTs were high for all serogroups.

Following the second dose of Menactra vaccine in children who received Menactra vaccine at 9 and 15 months of age, the percentage of participants with an hSBA titer >1:8 were high for all of the serogroups (>96% for C, Y and W-135 and >85.2% for serogroup A).

Individuals 2 through 55 Years of Age

Immunogenicity was evaluated in three comparative, randomized, US, multi-center, active controlled clinical trials that enrolled children (2 through 10 years of age), adolescents (11 through 18 years of age), and adults (18 through 55 years of age). Participants received a single dose of Menactra vaccine (N=2526) or Menomune – A/C/Y/W-135 vaccine (N=2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination. (Blinding procedures for safety assessments are described in **ADVERSE REACTIONS** section.)

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population.

Immunogenicity in Children 2 through 10 Years of Age

Of 1408 enrolled children 2 through 10 years of age, immune responses evaluated by hSBA in a subset of Menactra vaccine participants (2 through 3 years of age, N=52; 4 through 10 years of age, N=84) and Menomune – A/C/Y/W-135 vaccine participants (2 through 3 years of age, N=53; 4 through 10 years of age, N=84), the percentages of subjects with a titer ≥1:8 were constantly higher in the Menactra group for all four serogroups.

In the evaluated subset of participants 2 through 3 years of age, the percentage of participants with an hSBA titer ≥1:8 at Day 28 were 73%, Serogroup A; 63%, Serogroup C; 88%, Serogroup Y; 63%, Serogroup W-135 in the Menactra group and 64%, Serogroup A; 38%, Serogroup C; 73%, Serogroup Y; and 33%, Serogroup W-135 in the Menomune group.

In the evaluated subset of participants 4 through 10 years of age, the percentage of participants with an hSBA titer ≥1:8 at Day 28 were 81%, Serogroup A; 79% Serogroup C; 99%, Serogroup Y; 85%, Serogroup W-135 in the Menactra group and 55%, Serogroup A; 48%, Serogroup C; 92%, Serogroup Y; and 79%, Serogroup W-135 in the Menomune group.

Immunogenicity in Adolescents 11 through 18 Years of Age

Results from the comparative clinical trial conducted in 881 adolescents (aged 11 through 18 years) showed that the immune responses measured by SBA-BR to Menactra vaccine and Menomune – A/C/Y/W-135 vaccine were similar for all four serogroups.

The percentage of participants with an SBA-BR titer with a ≥4-fold rise from the baseline were 93%, Serogroup A; 92%, Serogroup C; 82%, Serogroup Y; 97%, Serogroup W-135 in the Menactra group and 92%, Serogroup A; 89%, Serogroup C; 80%, Serogroup Y; and 95%, Serogroup W-135 in the Menomune group.

In participants with undetectable pre-vaccination titers (ie, less than 1:8 at Day 0), seroconversion rates (defined as a ≥4-fold rise in Day 28 SBA-BR titers) were similar between the Menactra vaccine and Menomune – A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100% Serogroup A; 99%, Serogroup C; 98%, Serogroup Y; 99%, Serogroup W-135. The seroconversion rates for Menomune – A/C/Y/W-135 vaccine recipients were: 100%, Serogroup A; 99%, Serogroup C; 100%, Serogroup Y; 99%, Serogroup W-135.

Immunogenicity in Adults 18 through 55 Years of Age

Results from the comparative clinical trial conducted in 2554 adults aged 18 through 55 years showed that the immune responses measured by SBA-BR to Menactra vaccine and Menomune – A/C/Y/W-135 vaccine were similar for all four serogroups.

The percentage of participants with an SBA-BR titer with a ≥4-fold rise from the baseline were 81%, Serogroup A; 89%, Serogroup C; 74%, Serogroup Y; and 89%, Serogroup W-135 in the Menactra group and 85%, Serogroup A; 90%, Serogroup C; 79%, Serogroup Y; and 94%, Serogroup W-135 in the Menomune group.

In participants with undetectable pre-vaccination titers (ie, less than 1:8 at Day 0), seroconversion rates (defined as a ≥4-fold rise in Day 28 SBA-BR titers) were similar between the Menactra vaccine and Menomune – A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100%, Serogroup A; 99%, Serogroup C; 91%, Serogroup Y; and 97%, Serogroup W-135. The seroconversion rates for Menomune – A/C/Y/W-135 vaccine recipients were: 99%, Serogroup A; 98%, Serogroup C; 97%, Serogroup Y; and 99%, Serogroup W-135.

Concomitant Vaccine Administration

MMRV (or MMR + V) or PCV7

In a US, active-controlled trial, 1179 children received Menactra vaccine at 9 months and 12 months of age. At 12 months of age, these children received Menactra vaccine concomitantly with MMRV (N=616), or MMR + V (N=48), or PCV7 (N=250). Another group of 12-month old children received MMRV + PCV7 (N=485). Sera were obtained approximately 30 days after the last vaccinations. Measles, mumps, rubella and varicella antibody responses among children who received Menactra vaccine and MMRV (or MMR and V) were comparable to corresponding antibody responses among children who received MMRV and PCV7.

When Menactra vaccine was given concomitantly with PCV7, the non-inferiority criteria for comparisons of pneumococcal IgG GMCs (upper limit of the two-sided 95% CI of the GMC ratio ≤2) were not met for 3 of 7 serotypes (4, 6B, 18C).

In a subset of 196 (all subjects with available sera) who received Menactra vaccine and PCV7 concomitantly, sera was evaluated with pneumococcal opsonophagocytic assay (OPA) and >99% of the subjects had a titer well above the protective level of ≥1:8.

Td

In a double-blind, randomized, controlled trial, 1021 participants aged 11 through 17 years received Td and Menactra vaccines concomitantly (N=509), or Td followed one month later by Menactra vaccine (N=512). Sera were obtained approximately 28 days after each respective vaccination. The proportion of participants with a 4-fold or greater increase in SBA-BR titer to meningococcal Serogroups C, Y and W-135 was higher when Menactra vaccine was given concomitantly with Td (86-96%) than when Menactra vaccine was given one month following Td (65-91%). Anti-tetanus and anti-diphtheria antibody responses were similar in both study groups.

Typhim Vi (Typhoid Vi Polysaccharide Vaccine)

In a double-blind, randomized, controlled trial, 945 participants aged 18 through 55 years received Typhim Vi and Menactra vaccines concomitantly (N=469), or Typhim Vi vaccine followed one month later by Menactra vaccine (N=476). Sera were obtained approximately 28 days after each respective vaccination. The antibody responses to Menactra vaccine and to Typhim Vi vaccine components were similar in both study groups.

HOW SUPPLIED

Vial, 1 Dose (5 vials per package).
Vial, 1 Dose (1 vial per package).

STORAGE

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Do not use after expiration date.

INFORMATION FOR PATIENTS

Prior to administration of Menactra vaccine, the healthcare professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient (see **ADVERSE REACTIONS** and **WARNINGS AND PRECAUTIONS**). Patients, parents or guardians should be instructed to report any suspected adverse reactions to their healthcare professional who should report these events to Sanofi Pasteur Inc.

MENACTRA® is a registered trademark of sanofi pasteur and its subsidiaries.

Manufactured by:
Sanofi Pasteur Inc.
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Product Information as of
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