Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
MEMORANDUM

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Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: Merck Sharp & Dohme LLC

Product: GARDASIL 9

Submission Tracking Number (STN): 125508/2020

Indication(s): GARDASIL 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal, and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Meeting Date: Pediatric Advisory Committee Meeting, April 29 – 30, 2025

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the June 12, 2020, approval of GARDASIL 9 under submission tracking number (STN) 125508/868 to add the prevention of oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types targeted by the vaccine in men and women 9 through 45 years of age.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. GARDASIL 9 is a sterile suspension for intramuscular administration. Each dose of GARDASIL 9 is 0.5-mL. The U.S. prescribing information (USPI), Section 2.1, describes the following dosage by age:

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
9 through 14 years	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.

GARDASIL 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal, oropharyngeal, and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.3 Regulatory History

A summary of pertinent regulatory history is provided in table below.

Table 1: GARDASIL 9 Regulatory History

Date	STN	Approved indication(s)
December 10, 2014*	125508/0	Indicated in girls and women 9 through 26 years of age for prevention of the following diseases: • Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS) • Cervical intraepithelial neoplasia (CIN) grade 1 • Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 • Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 Indicated in boys 9 through 15 years of age for the prevention of the following diseases: • Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3
December 14, 2015	125508/15	Extend the indication by including boys and men 16 through 26 years of age for the prevention of the following diseases:

Date	STN	Approved indication(s)
		• Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3
October 7, 2016*	125508/153	To include a 2-dose regimen for individuals 9 through 14 years of age.
October 5, 2018	125508/493	To extend the age range for the use of the vaccine to include women and men from 27 to 45 years of age
June 12, 2020**	125508/868	To add prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine in men and women 9 through 45 years of age.

*A prior review of postmarketing safety data, covering December 10, 2014 – June 30, 2017, was completed in 2018 for the above PAC triggers (please see prior PAC safety and utilization review memorandum STN 125508/416).

**Regulatory trigger for current PAC review, covering June 12, 2020 – September 30, 2024, subject of this memorandum.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
  - VAERS reports for GARDASIL 9 during June 12, 2020, to September 30, 2024 (PAC review period)
- Manufacturer's Submissions
  - GARDASIL 9 U.S. package insert; updated September 2024
  - Applicant response to information request regarding dose distribution data, received under STN 125508/2020
  - Pharmacovigilance Plan, Version 6.0 dated November 1, 2022
  - Periodic safety reports
- FDA Documents
  - STN 125508/868 GARDASIL 9 approval letter
  - STN 125508/868 Pharmacovigilance Plan Review Memorandum
  - STN 125508/1706 GARDASIL 9 approval letter
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

During the PAC review period, the following label change was associated with postmarketing safety data:

- On March 14, 2024, a labeling supplement under STN 125508/1706 was approved to include information from the GARDASIL 9 pregnancy registry in support of updating the Package Insert and Patient Package Insert.

Following the PAC review period, the following label change was associated with postmarketing safety data:

- On March 25, 2025, a labeling supplement under STN 125508/1994 was approved to update Section 6.2 (Post marketing Experience, Adverse Reactions) of the package insert to include “injection-site nodule”.

4 PRODUCT UTILIZATION DATA

The sponsor provided the following GARDASIL 9 distribution data for the U.S. and worldwide for the time interval, June 1, 2020, to September 30, 2024:

- US: approximately 42.5 million doses distributed
- Worldwide: approximately 202.5 million doses distributed

The sponsor was not able to provide an estimate of the number of individuals vaccinated in pediatric and adult age groups. Note that the number of doses distributed is an estimate of the number of individuals vaccinated because doses may have been distributed without being administered to individuals or individuals may have received more than one dose (GARDASIL 9 may be administered as a 2-dose or 3-dose regimen).

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1. Pharmacovigilance Plan

The manufacturer’s current Pharmacovigilance Plan (PVP), Version 6.0, dated November 1, 2022, does not contain important identified or potential risks. “Long term effectiveness and immunogenicity” is listed as missing information.

Of note, in the previous PVP (Version 5.0), as described in the prior PAC review memorandum (STN 125508/416) the sponsor had included the following important identified risks: hypersensitivity, syncope with fall resulting in injury, and exposure during pregnancy. Hypersensitivity and syncope with fall are listed in the ‘Adverse Reactions’ section of the USPI, and syncope with fall is also listed in the USPI under ‘Warnings and Precautions.’ Important potential risks in the prior PVP had included viral type replacement, Guillain-Barre Syndrome (GBS), product confusion, and “mixed regimen” (i.e., a single patient receiving two or more different types of HPV vaccine in a series), and each of these risks are monitored via a postmarket extension study, V503-

021: Nordic Long-Term Follow-Up Study (10-year extension in subjects from V503-001). Clinical trial V503-001 was conducted prior to Gardasil 9 approval to assess and compare the efficacy and safety of Gardasil to that of Gardasil 9 in young women aged 16-26 years. Postmarketing surveillance study V503-021 enrolled patients from V503-001 in Nordic Region countries (approximately 4500 subjects) into a registry-based long-term follow up study to evaluate safety, immunogenicity, and effectiveness. The final report is planned for December 2026. Finally, the risks associated with exposure during pregnancy were characterized via the sponsor's completed pregnancy registry.

Regarding the current PVP (Version 6.0), according to the sponsor: "*Based on scientific information to date and the latest guidance on Risk Management Planning from the EMA [European Medicines Agency], the Important Identified and Potential Risks have been removed:*

- *Analysis of the post-marketing data gathered on 9vHPV vaccine shows that there are no outstanding additional pharmacovigilance activities to address the previous identified and potential risks listed in the RMP [Risk Management Plan]*
- *The risks are fully characterized and appropriately managed through labelling*
- *There is no reasonable expectation that any pharmacovigilance activity can further characterize the previously listed Important identified and potential risks."*

The safety profile of GARDASIL 9 is monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. The sponsor's ongoing and completed safety-related postmarketing commitment (PMC) studies for GARDASIL 9 are described in section 5.2 of this memorandum. GARDASIL 9 does not have a safety-related postmarketing requirement (PMR) study under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) or a Risk Evaluation and Mitigation Strategy (REMS).

5.2 Safety-related Postmarketing Studies

The following safety-related postmarketing studies were described in GARDASIL 9 STN 125508/0 approval letter dated December 10, 2014:

Postmarketing commitments (PMCs)
PMC#1, Study V503-002-20: To complete the ongoing 10-year study extension to clinical trial V503-002 to evaluate the long-term safety, immunogenicity, and effectiveness of GARDASIL 9 in males and females who were between 9 and 15 years of age at enrollment.
Study status: Completed, and the final study report did not identify any new safety concerns (STN 125508/1434 PMC fulfillment and supplement approval).

PMC#2, Study V503-021: To conduct a 10-year study extension of Protocol V503-001 (Nordic Region countries of Denmark, Norway, and Sweden) to evaluate the long-term safety, immunogenicity, and effectiveness of GARDASIL 9 in women who were 16 to 26 years of age at enrollment.
Study status: Ongoing (upcoming study milestone dates include Study Completion: June 30, 2026; Final Report Submission: December 31, 2026).

PMC#3: To conduct an observational study to further characterize the safety profile of GARDASIL 9 in approximately 10,000 persons.
Study status: Completed, and the final study report did not identify any new safety concerns (STN 125508/867).

PMC#4: To establish a pregnancy registry, to be continued for at least 5 years, to prospectively collect data on spontaneously reported exposures to GARDASIL 9 occurring within 30 days prior to the last menstrual period or at any time during pregnancy.
Study status: Completed, and the final study report did not identify any new safety concerns. The label was updated with pregnancy safety data (STN 125508/1706).

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of GARDASIL 9 between June 12, 2020, to September 30, 2024 (PAC review period). VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for GARDASIL 9 during the PAC review period are listed in Table 2 below. There were 8,015 US and 2,131 foreign reports for the review period June 12, 2020, to September 30, 2024.

Table 2: GARDASIL 9 VAERS reports during June 12, 2020, to September 30, 2024

Age	U.S. Serious Non-Fatal*	Foreign Serious Non-Fatal*	U.S. Deaths	Foreign Deaths	U.S. Non-Serious	Foreign Non-Serious	U.S. Total Reported	Foreign Total Reported
<18 years	333	734	6	2	4258	10	4597	746
≥ 18 years	130	590	5	4	1699	24	1834	618
Unknown	94	524	1	7**	1489	236	1584	767
All Ages	557	1848	12	13	7446	270	8015	2131

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
**Note: Based on review of case narratives, two of the reports with "unknown age" in Table 2 were determined to involve pediatric patients.

1.3.1 Deaths

There were 21 unique deaths, described in 25 reports, during the PAC review period, including 8 unique pediatric deaths (5 U.S. and 3 foreign pediatric deaths). These reports were individually reviewed and are summarized below. Review of death reports (including 8 unique pediatric deaths (5 US and 3 foreign) did not identify patterns suggesting new safety concerns for GARDASIL 9. The frequency of reports resulting in death was low compared to the overall use of this vaccine (as described in section 4 of this memorandum, with more than 40 million doses in the U.S., and more than 200 million doses distributed worldwide). Alternate etiologies were provided in some cases (as documented in below narratives), and the causes of death varied with no single predominant cause; and, although rare, many of the conditions in these reports can occur in the populations in which this vaccine is used, regardless of exposure to a vaccine.

Pediatric death reports

U.S. pediatric death reports (6 reports for 5 unique cases)

- 14-year-old male received GARDASIL 9 and influenza vaccine and died 5 days later. Medical history complicated by autism and coarctation of the aorta with prior surgical repair. Autopsy revealed a bicuspid aortic valve hypertrophy and pulmonary consolidations. Cultures grew Enterobacter cloacae and Klebsiella oxytoca.
  Reviewer comments: An infectious etiology is likely given the available information.

- 12-year-old female with a history of asthma, depression, ADHD, and migraines received GARDASIL 9, COVID-19 vaccine, Menactra, and TDaP vaccines. She presented to a neurologist 8 days after vaccination with headache, dizziness, nausea/vomiting, and photophobia. Her neurologic exam was unremarkable, and she was diagnosed with migraines and prescribed Ibuprofen. Twenty-six days following vaccination, she presented to the ED with a severe headache, dizziness and vomiting followed by sudden

cardiopulmonary arrest; she was intubated and died shortly after arrival in the ED. The autopsy demonstrated cerebellar tonsillar and bilateral uncal herniation.
Reviewer comments: Additional clinical information on brain imaging or laboratory test results (for example, tests to rule out any infectious etiology) during her presentation to the ED was not available, and definitive assessment of causal association with GARDASIL 9 is not possible.

- 10-year-old female received GARDASIL 9 and developed headaches, fever, cough, and fatigue two weeks later. She was later admitted to a hospital 10 weeks post-vaccination and diagnosed with acute encephalitis associated with anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody production and received immune globulins. She suffered a cerebral edema and tonsillar herniation and died. Autopsy demonstrated multicompartmental inflammatory reactive changes compatible with MOG antibody disease, brain swelling and central/tonsillar herniation, and multifocal brain and brainstem necrosis. Of note, per report she had recently recovered from an upper respiratory tract infection and classmates had tested positive for RSV a few weeks after her vaccination. Her viral testing in the hospital (Covid, influenza, RSV) was negative.
  Reviewer comments: Cause of death was attributed to autoimmune encephalitis and MOG antibody disease as per autopsy. Anti-MOG antibody-associated disease may occur post-infection and has been described in case reports in literature after various vaccines or may be seen in association with acute disseminated encephalomyelitis (ADEM). In this case, the patient is reported to have had an URI, which may represent an infectious etiology as the precipitant of her symptoms. Of note, ADEM is included in the Postmarketing Experience section of the USPI.

- Literature case report[1] of 14-year-old male who received GARDASIL 9 and reported a headache three weeks later. Forty days post vaccination, he developed left-sided weakness, urinary incontinence, and altered mental status. He was diagnosed with acute demyelinating encephalomyelitis (ADEM) and died. Neuropathologic examination revealed an acute vascular inflammatory process and findings consistent with acute hemorrhagic leukoencephalitis (AHLE). The authors postulate that molecular mimicry may be a biologically plausible mechanism by which GARDASIL 9 may trigger demyelinating disease.
  Reviewer comments: As per the sponsor, based on the available information, the causal relationship between GARDASIL 9 and acute hemorrhagic leukoencephalitis is assessed as indeterminate and limited information regarding concomitant medications and/or vaccinations, any preceding illnesses, evaluation for differential diagnosis, and additional clinical details, precludes definitive assessment of a causal association to immunization. AHLE is considered the most severe form of ADEM. Of note, ADEM is

[1] Reference: Wellnitz K, Sato Y, Bonthius DJ. Fatal Acute Hemorrhagic Leukoencephalitis Following Immunization Against Human Papillomavirus in a 14-Year-Old Boy. Child Neurol Open. 2021 May 18;8:2329048X211016109. doi: 10.1177/2329048X211016109. PMID: 34046515; PMCID: PMC8135193.

included in the *Postmarketing Experience* section of the USPI.

- 11-year-old female was diagnosed with leukemia one year after receiving GARDASIL 9 and Menactra and died of multi-organ failure secondary to graft-versus-host disease.
  Reviewer comment: Cause of death is related to underlying disease.

Foreign pediatric death reports (3 cases)

- 13-year-old female* received GARDASIL 9 and developed symptoms of anaphylaxis 15 minutes following vaccination. She received epinephrine and was transported to a hospital for further treatment 45 minutes after receiving the vaccine and died. (An additional report of this case was received as "age unknown" and upon review of the narrative, it was ascertained to be a duplicate report of this case.)
  Reviewer comment: The USPI includes a *Warning* on *Managing Allergic Reactions* and includes *hypersensitivity reactions including anaphylactic/anaphylactoid reactions* under *Postmarketing Experience*.
- A 16-year-old (sex unknown) was vaccinated with GARDASIL 9 and died on an unknown date. This report was subsequently deemed 'non-valid' as there was no contactable reporter.
  Reviewer comment: Lack of clinical information precludes assessment.

- 10-year-old male* received GARDASIL 9 and reported to have developed encephalitis, a neurodegenerative disorder and cerebral atrophy with unknown time to onset post vaccination. He died four years following vaccination. (*Was listed initially as "unknown age" but review of the narrative indicated patient age.)
  Reviewer comments: Additional information provided by the sponsor indicates onset of neuropsychiatric condition preceded vaccine administration. Lack of additional clinical details on underlying conditions, concomitant medications, clinical course, and timeline for presentation of symptoms, precludes assessment of casual association.

<u>Adult death reports</u>
During the PAC review period, there were 9 adult death reports (5 U.S. reports and 4 foreign reports).

U.S. adult death reports (5 reports for 3 unique cases) included a case of metastatic cervical carcinoma, and two cases of cardiac arrest. The cases were complicated by underlying conditions and none of the cases were attributed to vaccination based on the available reported information and the patients' medical history per FDA review.

Foreign adult death reports (4) included two cases with no clinical details for review, one case of pulmonary hypertension and death due to advanced heart failure, and one case of renal failure in a patient with underlying lupus.

Death reports: patient age unknown

Patient age was unknown for the remaining 8 death reports (1 U.S. report and 7 foreign reports), which represented 5 unique cases. These cases included cardiac arrest (n = 1), breast cancer (n = 1), and the three remaining cases lacked clinical details and did not provide information on cause of death.

1.3.2 Serious Non-fatal Reports

During the PAC review period, there were 2,405 serious non-fatal reports, including 1,067 pediatric reports and 720 adult reports. Age was unknown for the remaining 618 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for pediatric (Table 3) and adult (Table 4) are displayed below. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Top 30 PTs for pediatric (< 18 years) serious reports

Preferred Term (PT)	**# Serious Pediatric Reports**	**Label Status** *USPI update 09/2024 (Label Section)*
Headache	174	Labeled (6.1 Clinical Trials Experience)
Syncope	173	Labeled (5.1 Warnings and Precautions)
Dizziness	154	Labeled (6.1 Clinical Trials Experience)
Loss of consciousness	150	Not labeled (Note that Syncope is labeled under 5.1 Warnings and Precautions)
Fatigue	136	Labeled (6.1 Clinical Trials Experience)
Nausea	115	Labeled (6.1 Clinical Trials Experience)
Pyrexia	106	Labeled (6.1 Clinical Trials Experience)
Malaise	90	Labeled (6.2 Postmarketing Experience)
Seizure	75	Labeled (6.2 Postmarketing Experience)
Vomiting	75	Labeled (6.2 Postmarketing Experience)
Pain	74	Not labeled (Note that injection site pain is labeled under 6.1 Clinical Trials Experience)
Asthenia	72	Labeled (6.2 Postmarketing Experience)
Pallor	67	Not labeled
Rash	60	Not labeled
Dyspnea	58	Not labeled
Pain in extremity	57	Not labeled
Hypoaesthesia	51	Not labeled

Preferred Term (PT)	# Serious Pediatric Reports	Label Status *USPI update 09/2024 (Label Section)*
Loss of personal independence in activities	51	Not labeled
Fall	50	Labeled (5.1 Warnings and Precautions)
Presyncope	49	Not labeled
Arthralgia	48	Labeled (6.2 Postmarketing Experience)
Abdominal pain	46	Labeled (6.1 Clinical Trials Experience)
Postural orthostatic tachycardia syndrome	43	Not labeled
Condition aggravated	42	Not labeled
Paresthesia	42	Not labeled
Muscular weakness	41	Not labeled
Tremor	39	Not labeled
Gait disturbance	36	Not labeled
Anxiety	33	Not labeled
Erythema	33	Not labeled (Note that injection site erythema is labeled under 6.1 Clinical Trials Experience)

Reviewer comments: Most frequently reported PTs are labeled events or related to labeled events as noted in above table. Unlabeled PTs such as *Presyncope, Pallor, Loss of consciousness, Tremor, Gait disturbance, Postural orthostatic tachycardia syndrome* are likely related to the labeled event of syncope.

Reports of “Postural Orthostatic Tachycardia Syndrome” (POTS) were reviewed. Many cases of POTS were also associated with the PTs “dizziness,” “fainting,” “pre-syncope”, “syncope,” “headaches,” and “fatigue.” Preceding medical histories included diabetes, asthma, anxiety, fibromyalgia, chronic pain syndrome (CPS), thyroid disease, chronic constipation, attention deficit hyperactivity disorder (ADHD), and anorexia. 13 patients had received multiple vaccines and >90% were girls. Review of the reports demonstrated no clustering or discernible patterns. POTS has an incidence of 1 in 1000 people and is more commonly diagnosed in women between the age of 15 and 50. POTS is characterized by an excessive tachycardia upon standing in the absence of concurrent hypotension. Additional symptoms include lightheadedness, palpitations, blurry vision, fatigue, headaches, chronic pain, generalized weakness, and tremulousness. The European Medicines Authority (EMA) published a review article in 2015 which examined the relationship between the HPV vaccines and chronic regional

pain syndrome (CRPS) and/or POTS disease.[2] The authors examined pharmacovigilance data, published literature, and information submitted by the public and concluded that no evidence currently exists that would demonstrate a causal association between the HPV vaccines and the development of POTS and/or CRPS.

Unlabeled non-specific PTs include *Rash, Dyspnea, Hypoesthesia, Paraesthesia, Condition aggravated, Loss of personal independence in activities. Rash* may be related to labeled events for *Urticaria*, *Cellulitis, Hypersensitivity reactions including anaphylactic/anaphylactoid reactions* (USPI section 6.2). Review of reports of *Muscular weakness* revealed no clustering or discernable patterns. Review of reports of *Anxiety* revealed no clustering or discernable patterns; many of these cases were also associated with post-vaccination syncope.

Comparison with the prior PAC review of postmarketing data (PAC safety and utilization review memorandum STN 125508/416) revealed a similar list of PTs. Overall, no unusual frequency, clusters, or other trends for adverse events were identified from review of the serious reports. No new safety concerns were identified.

Table 4: Top 20 PTs for adult (18 years and older) serious reports

Preferred Term (PT)	**# Serious Reports**	**Label Status** *USPI update 09/2024 (Label Section)*
Pyrexia	86	Labeled (6.1 Clinical Trials Experience)
Dizziness	77	Labeled (6.1 Clinical Trials Experience)
Headache	70	Labeled (6.1 Clinical Trials Experience)
Pain	58	Not labeled (Note that injection site pain is labeled under 6.1 Clinical Trials Experience)
Hypoesthesia	55	Not labeled
Arthralgia	54	Labeled (6.2 Postmarketing Experience)
Fatigue	52	Labeled (6.1 Clinical Trials Experience)
Nausea	52	Labeled (6.1 Clinical Trials Experience)
Hypersensitivity	47	Labeled (6.2 Postmarketing Experience)
Pain in extremity	47	Not labeled
Syncope	47	Labeled (5.1 Warnings and Precautions)
Loss of consciousness	46	Not labeled (Note that Syncope is labeled under 5.1 Warnings and Precautions)
Paresthesia	44	Not labeled

[2] 11 November 2015 EMA/762033/2015 Pharmacovigilance Risk Assessment Committee (PRAC

Preferred Term (PT)	# Serious Reports	Label Status *USPI update 09/2024 (Label Section)*
Rash	42	Not labeled
Asthenia	41	Labeled (6.2 Postmarketing Experience)
Vomiting	39	Labeled (6.2 Postmarketing Experience)
Dyspnea	32	Not labeled
Muscular Weakness	31	Not labeled
Myalgia	28	Labeled (6.2 Postmarketing Experience)
Diarrhea	27	Labeled (6.1 Clinical Trials Experience)

Reviewer comments: Most PTs are labeled events or related to labeled events or represent non-specific events and have been previously discussed.

1.3.3 Non-serious Reports

During the reporting period, there were 7,716 non-serious reports; of which 4268 involved pediatric individuals. Table 5 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 5: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *USPI update 09/2024 (Label Section)*
No adverse event	2214	N/A
Product storage error	1038	N/A
Dizziness	709	Labeled (6.1 Clinical Trials Experience)
Syncope	637	Labeled (5.1 Warnings and Precautions)
Inappropriate schedule of product administration	625	N/A
Product administered to patient of inappropriate age	524	N/A
Pallor	421	Not labeled
Wrong product administered	407	N/A
Loss of consciousness	401	Not labeled (Note that Syncope is labeled under 5.1 Warnings and Precautions)
Nausea	389	Labeled (6.1 Clinical Trials Experience)
Injection site pain	330	Labeled (6.1 Clinical Trials Experience)

Reviewer comments: Most of the above unlabeled PTs reflect product use issues and medication errors (including product storage error, inappropriate schedule of product administration, product administered to a patient of inappropriate age, wrong product administered). These errors are not linked with a clinical adverse event. The reviewer confirmed that these errors were almost always associated with the PT "no adverse event," suggesting that no harm came to the patient.

The PT "product storage error" detailed temperature excursions that occurred because of refrigerator failures or power outages in different geographical regions. Over 90% of these cases also included the PT "No adverse event."

For the PT 'Wrong product administered' patients received a variety of other vaccinations (for example, Pneumovax and Prevnar) instead of the intended GARDASIL 9, or in other reports, individuals received GARDASIL 9 instead of other intended vaccines (including Prevnar, Menquadfi, etc.). Some reports described clinicians providing the wrong tetanus vaccine (DTAP instead of TDAP), in addition to the correctly ordered GARDASIL 9 vaccine, i.e., the administration error was unrelated to GARDSASIL 9. Most of these cases also included the PT "No adverse event."

Regarding the PT "inappropriate schedule of product administration" the providers provided the second or third doses either earlier or later than the indicated schedule. Again, over 90% of these cases also included the PT "No adverse event." Of note, the product administration schedule is found in "Dosage and Administration" of the USPI.

For the PT "product administered to patient of inappropriate age" the healthcare providers administered GARDASIL 9 to patients outside of the approved age range. Over 90% of these cases also included the PT "No adverse event." The approved age range for GARDASIL 9 is in the section "Indications and Usage" of the USPI.

The other frequently reported non-serious PTs listed above (dizziness, syncope, nausea, injection site pain) reflect adverse events that are labeled in the USPI. Although loss of consciousness is not labeled, syncope is found in Section 5.1 in "Warnings and Precautions."

1.4 Data mining

Data mining was performed to evaluate whether any reported events following the use of GARDASIL 9 were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of November 1, 2024, for HPV (GARDASIL 9) identified the following PTs (displayed below) with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

PTs describing syncope and related events
The following PTs describe syncope, or are related to syncope, which is a well-known phenomenon in children who receive vaccinations and is a labeled event for GARDASIL 9 (included under Section 5.1 Warnings and Precautions): *Syncope; Presyncope; Psychogenic pseudosyncope; Loss of consciousness; Pallor; Posture abnormal; Immediate post-vaccine reaction; Seizure-like phenomena; Tonic clonic movements.* Additional PTs of events that may result from syncope include *Fall; Head injury; Face injury;* and *Skin laceration.*

PTs that do not represent clinical adverse events:
The following PTs describe variations in the recommended vaccination schedule/regimen or product quality issues and do not represent adverse events: *Inappropriate schedule of product administration; Product prescribing issue; Syringe issue; Poor quality device used; and Interchange of vaccine products.*

PTs related to pregnancy that did not represent AEs included *Pregnancy test positive*; *Pregnancy test urine positive*, and *Exposure during pregnancy*, and reflect inadvertent vaccination of a pregnant individual. These PTs are associated with the indicated population, that includes women of childbearing age, for use of GARDASIL 9; one would expect them to be disproportionally reported when compared to other vaccines in VAERS.

PTs that represent confounding by indication: *Smear cervix abnormal; Human papilloma virus test positive; Anogenital warts; Skin papilloma; Papilloma viral infection.* GARDASIL 9 is indicated to prevent anogenital disease. These PTs are associated with the indicated population for use of GARDASIL 9; one would expect them to be disproportionally reported when compared to other vaccines in VAERS.

Other PTs
- *Ill-defined disorder* represents non-specific events.
- *Hormone therapy* represents a treatment and not an adverse event.

1.5 Periodic safety reports
The manufacturer's postmarketing periodic safety reports for GARDASIL 9 were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on 30 October 2024 for peer-reviewed literature, with the search term "GARDASIL 9" and "safety" limited by human species, and dates from PAC trigger (June 12, 2020) to date of search October 30, 2024, retrieved 12 publications. After reviewing the titles and abstracts of these articles, and excluding articles summarizing efficacy data, dosing regimens, or other issues, there were 3 publications pertinent to safety of GARDASIL 9. No new safety concerns for GARDASIL 9 were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Soliman M, Oredein O, Dass CR. Update on Safety and Efficacy of HPV Vaccines: Focus on Gardasil. Int J Mol Cell Med. 2021 Spring;10(2):101-113. doi: 10.22088/IJMCM.BUMS.10.2.101. Epub 2021 Sep 1. PMID: 34703794; PMCID: PMC8496244	The authors reviewed safety data on GARDASIL and GARDASIL 9 by conducting a literature search, which deemed the vaccines to be safe and efficacious.
Bianchi FP, Tafuri S, Stefanizzi P. Real-Life Safety Profile of the 9-Valent HPV Vaccine Based on Data from the Puglia Region of Southern Italy. Vaccines (Basel). 2022 Mar 10;10(3):419. doi: 10.3390/vaccines10030419. PMID: 35335051; PMCID: PMC8948997.	The authors conclude that GARDASIL 9 safety profile appears to be favorable, with a low rate of serious adverse events.
Vaccine in Pregnancy With Spontaneous Abortion and Adverse Birth Outcomes. JAMA Netw Open. 2021 Apr 1;4(4):e214340. doi: 10.1001/jamanetworkopen.2021.4340. PMID: 33818618; PMCID: PMC8022219.	This cohort study analyzed data from 7 participating health systems in the Vaccine Safety Datalink. The cohort comprised pregnancies among girls and women aged 12 to 28 years that ended between October 26, 2015, and November 15, 2018. Singleton pregnancies that ended in a live birth, stillbirth, or spontaneous abortion were included. This study found that 9vHPV vaccine exposures during or around the time of pregnancy were uncommon and not associated with spontaneous abortions or selected adverse birth outcomes. These findings can inform counseling for inadvertent 9vHPV vaccine exposures.

8 CONCLUSION

This post marketing pediatric safety review was triggered by the June 12, 2020, approval of STN 125508/868 to add prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine in men and women 9 through 45 years of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for GARDASIL 9 does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency,

clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of GARDASIL 9.