

**Public Assessment Report**  
**(Variation, 2 doses schedule)**

**GARDASIL 9**

**INFORMASI PRODUK**

Nama obat	:	Gardasil 9
Bentuk sediaan	:	Suspension for injection
Zat aktif	:	Vaksin human papilloma virus 9 valent (recombinant adsorbed) dimana setiap dosis (0,5 mL) mengandung: <ul style="list-style-type: none"><li>- HPV tipe 6 protein L1 - 30 mikrogram</li><li>- HPV tipe 11 protein L1 - 40 mikrogram</li><li>- HPV tipe 16 protein L1 - 60 mikrogram</li><li>- HPV tipe 18 protein L1 - 40 mikrogram</li><li>- HPV tipe 31 protein L1 - 20 mikrogram</li><li>- HPV tipe 33 protein L1 - 20 mikrogram</li><li>- HPV tipe 45 protein L1 - 20 mikrogram</li><li>- HPV tipe 52 protein L1 - 20 mikrogram</li><li>- HPV tipe 58 protein L1 - 20 mikrogra</li></ul>
Kemasan	:	Dus, 10 prefilled syringe @ 0,5 mL
Pendaftar	:	PT. Merck Sharp Dohme Pharma Tbk, Indonesia
Produsen	:	Merck Sharp & Dohme Corp., West Point, USA, untuk MSD BV., Haarlem, Netherland
Kategori Registrasi	:	Registrasi Variasi Perubahan Indikasi dan Posologi
Indikasi yang diajukan:	:	<p><i>Girls and Women</i></p> <p><i>GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:</i></p> <ul style="list-style-type: none"><li>- <i>Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58</i></li><li>- <i>Genital warts (condyloma acuminata) caused by HPV types 6 and 11</i></li></ul> <p><i>And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16,18, 31, 33, 45, 52, and 58.</i></p> <ul style="list-style-type: none"><li>- <i>Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)</i></li><li>- <i>Cervical intraepithelial neoplasia (CIN) grade 1</i></li><li>- <i>Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3</i></li><li>- <i>Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3</i></li><li>- <i>Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3</i></li></ul> <p><i>Boys and Men</i></p> <p><i>GARDASIL 9 is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases:</i></p> <ul style="list-style-type: none"><li>- <i>Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58</i></li><li>- <i>Genital warts (condyloma acuminata) caused by HPV types 6 and 11</i></li></ul> <p><i>And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16,18, 31, 33, 45, 52, and 58:</i></p>

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

*The use of Gardasil 9 should be in accordance with official recommendations. **Protection has been observed for up to 6 years (median duration of follow-up of 4 years) in a clinical study.** There are no data on the efficacy of Gardasil 9 beyond 6 years*

Posologi yang diajukkan : *The primary vaccination course consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.*

*The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.*

***Alternatively, in individuals 9 through 14 years of age, GARDASIL 9 can be administered according to a 2-dose schedule. The second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.***

*The need for a booster dose has not been established.*

*It is recommended that individuals who receive a first dose of Gardasil 9 complete the vaccination course with Gardasil 9.*

*Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for Gardasil 9.*

*Subjects previously vaccinated with a 3-dose regimen of quadrivalent HPV types 6, 11, 16, and 18 vaccine (Gardasil), hereafter referred to as qHPV vaccine, may receive 3 doses of Gardasil 9.*

*Paediatric population (children <9 years of age)*

*The safety and efficacy of Gardasil 9 in children below 9 years of age have not been established. No data is available.*

*Woman population  $\geq$  27 years of age*

*The safety and efficacy of Gardasil 9 in women 27 years of age and older have not been studied.*

*Method of administration*

*The vaccine should be administered by intramuscular injection. The preferred site is the deltoid area of the upper arm or in the higher anterolateral area of the thigh.*

*Gardasil 9 must not be injected intravascularly, subcutaneously or intradermally. The vaccine should not be mixed in the same syringe with any other vaccines and solution.*

Gardasil 9 merupakan vaksin yang mengandung *human papilloma virus 9 valent (recombinant adsorbed)* yang disetujui untuk indikasi pencegahan penyakit yang disebabkan oleh HPV tipe 6, 11, 16,18, 31, 33, 45, 52, dan 58 pada perempuan dan laki-laki usia 9 hingga 26 tahun. Saat ini diajukan penambahan posologi terkait penggunaan pada rentang usia 9-14 tahun dapat diberikan jadwal 2 dosis.

## **ASPEK MUTU**

Tidak ada evaluasi aspek mutu yang dilakukan, mengingat produk sudah terdaftar dan diajukan untuk penambahan indikasi / posologi yang tidak terkait mutu.

## **ASPEK KHASIAT KEAMANAN**

### **Studi non klinik**

Tidak ada evaluasi studi non klinik yang dilakukan.

### **Studi klinik**

Diserahkan 1 studi klinik fase 3 (P010) tolerabilitas dan immunogenisitas 2 dosis regimen V503, yang diadministrasikan pada subyek *preadolescents dan adolescents* ( 9 hingga 14 tahun) dibandingkan dengan Perempuan usia 16-26 tahun. Studi ini merupakan studi fase III, open label international, multicenter dengan jumlah total 1500 subjek.

Hasil evaluasi terhadap studi diatas yaitu

- Immunogenisitas pemberian Gardasil 9 pada usia 9-14 tahun dua dosis regimen 0,6 atau 0,12 pada laki laki dan perempuan, non inferior dibanding perempuan usia 16-26 tahun regimen 3 dosis terlihat dari GMT dan serokonversi. .
  - Satu bulan setelah pemberian dosis terakhir seropositif seluruh kelompok sebesar 97,9% - 100%. GMT (Geometric Mean Titers) satu bulan setelah dosis vaksin terakhir secara numerik lebih rendah untuk beberapa tipe vaksin setelah jadwal 2 dosis kelompok laki-laki usia 9-14 tahun dibandingkan dengan kelompok perempuan usia 9-14 tahun setelah jadwal 3 dosis. perlindungan jadwal 2 dosis gardasil 9 belum ditetapkan (HPV tipe 18, 31, 45, dan 52 untuk jadwal 0, 6 bulan serta HPV tipe 45 untuk jadwal 0, 12 bulan).
  - One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types.  
In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 12). The clinical relevance of these findings is unknown.  
Duration of protection of a 2-dose schedule of GARDASIL 9 has not been established.
- TAMBAHKAN TABEL 6

- Kejadian efek samping lebih sedikit pada usia 9-14 tahun dibanding 16-26 tahun, yaitu reaksi di tempat injeksi (pembengkakan, eritema), sakit kepala, dan demam. YAITU ... ambil dr SPC

## **EVALUASI**

### **Penilaian manfaat risiko**

Gardasil 9 merupakan vaksin yang mengandung *human papilloma virus 9 valent (recombinant adsorbed)* yang disetujui untuk indikasi pencegahan penyakit yang disebabkan oleh HPV tipe 6, 11, 16,18, 31, 33, 45, 52, dan 58 pada perempuan dan laki-laki usia 9 hingga 26 tahun. Saat ini diajukan penambahan posologi terkait penggunaan pada rentang usia 9-14 tahun dapat diberikan jadwal 2 dosis. Untuk Aspek mutu tidak dievaluasi lagi ada pengajuan ini.

Vaksin Gardasil 9 (jadwal 2 dosis) memiliki efek menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut.

- a. Efek yang menguntungkan:
  1. Imunogenisitas pemberian Gardasil 9 pada usia 9-14 tahun dua dosis regimen 0,6 atau 0,12 pada laki laki dan perempuan, non inferior dibanding perempuan usia 16-26 tahun regimen 3 dosis terlihat dari GMT dan serokonversi
  2. Kejadian efek samping lebih sedikit pada usia 9-14 tahun dibanding 16-26 tahun
- b. Efek yang tidak menguntungkan:
  1. Kejadian efek samping penggunaan GARDASIL 9 adalah reaksi pada lokasi injeksi seperti nyeri, bengkak dan kemerahan (84,8% penerima vaksin dalam 5 hari setelah kunjungan vaksinasi apa pun) dan sakit kepala (13,2% penerima vaksin dalam 15 hari setelah kunjungan vaksinasi apa pun).
- c. Ketidakpastian dan keterbatasan
  1. Kemanfaatan jangka Panjang Gardasil dengan jadwal 2 dosis pada subgroup usia 9-14 tahun masih terbatas.

#### **Kesimpulan manfaat-risiko**

Gardasil 9 dengan jadwal 2 dosis pada usia 9-14 tahun memiliki manfaat yang signifikan, termasuk imunogenisitas yang non-inferior dibandingkan regimen 3 dosis pada usia 16-26 tahun dan efek samping yang lebih sedikit. Meskipun terdapat ketidakpastian terkait durasi perlindungan jangka panjang, manfaatnya secara keseluruhan melebihi risikonya

## **KEPUTUSAN**

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi GARDASIL 9 **diterima dengan indikasi dan posologi** (*2 dose schedule*) sebagai berikut:

### **Indikasi**

#### *Girls and Women*

*GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the 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*

#### *Boys and Men*

*GARDASIL 9 is indicated in boys and men 9 through 26 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*

*The use of Gardasil 9 should be in accordance with official recommendations. Protection has been observed for up to 6 years (median duration of follow-up of 4 years) in a clinical study. There are no data on the efficacy of Gardasil 9 beyond 6 years*

### **Posologi**

*The primary vaccination course consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.*

*The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.*

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