

# Quadrivalent human papillomavirus vaccine (Gardasil)

## Summary

- The quadrivalent human papillomavirus (HPV) vaccine protects against infection with HPV types 6, 11, 16 and 18, which are responsible for 70% of cervical cancers and at least 90% of cases of genital warts.
- The vaccine is available under the National Immunisation Program (NIP) to females aged 12–26 years. It will be given in schools to girls aged 12–13 years on an ongoing basis. It will also be available to females aged 13–26 years in a 2-year, NIP-funded catch-up program — through schools for those up to the age of 18 years, and through general practice for those up to the age of 26 years.
- All girls and women who have been vaccinated must continue to have regular Pap smears because the vaccine does not protect against all HPV types that cause cervical cancer, or cervical cancer caused by HPV infection acquired before vaccination.
- Injection-site reactions (redness, swelling and pain) and mild systemic reactions (low-grade fever) are the most common adverse effects of the quadrivalent HPV vaccine.

## NIP listing

The quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine is available under the National Immunisation Program (NIP) for females aged 12–26 years. The vaccine will be given in schools to girls aged 12–13. The vaccine will also be available to females up to the age of 26 years through a catch-up program — for girls up to 18 years of age mainly through schools, and for women up to 26 years through general practice.<sup>1</sup> The catch-up program will run for the first 2 years of the vaccine's availability on the NIP.<sup>1</sup>

For information about the program and vaccine supply, contact the health department in your State or Territory. Contact details are available from the Immunise Australia Program website ([www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/home](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/home)).

People who wish to be vaccinated but are not eligible to receive the vaccine under the NIP will need to pay about \$460 for the 3-dose course.<sup>1</sup>

## Reason for NIP listing

The Pharmaceutical Benefits Advisory Committee rejected the first application for listing on the basis of uncertain and unacceptable cost-effectiveness.<sup>2</sup> Among

its considerations the PBAC noted that the total cost of a vaccination program would be large, yet the magnitude of benefit per patient was small (reducing lifetime cervical cancer risk from 0.78% to 0.38% for girls vaccinated at 12 years) and would not be apparent for many years. The Committee's concerns also included:

- the uncertainty about the treatment effect in sexually active women
- the possible adverse impact of reduced participation in cervical screening
- the need for a registry to help identify vaccinated women if booster doses were required
- the applicability of the trial population to the general Australian population.

A subsequent application was accepted on the basis of acceptable cost-effectiveness after a price reduction and resolution of some areas of uncertainty.<sup>3</sup> In particular, the sponsor committed funds to assist with establishing a registry of vaccinated women and agreed to new pricing arrangements if a booster dose is required.<sup>3</sup>

A more comprehensive discussion of the PBAC's deliberations is available in the public summary document ([www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-gardasil-nov06](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-gardasil-nov06)).

## New vaccine role for PBAC

The PBAC became responsible for making recommendations for funding of vaccines under the NIP in January 2006. Previously the Australian Technical Advisory Group on Immunisation (ATAGI) fulfilled this role. ATAGI continues to provide technical advice about vaccines to the PBAC and the Minister for Health and Ageing. However, the process for listing vaccines on the NIP now mirrors the process for medicines on the PBS, with a company seeking listing making a submission to the PBAC, who consider the cost-effectiveness of the new vaccine and make a recommendation to the Minister.

ATAGI also produces the *Australian Immunisation Handbook* ([www.immunise.health.gov.au](http://www.immunise.health.gov.au) then follow the link on the right side of the screen). The 9th edition is expected to be published in mid-2007.

## Place in therapy

The quadrivalent HPV vaccine protects against infection with HPV types 6, 11, 16 and 18, which are responsible for 70% of cervical cancers and 90% of cases of genital warts.

The vaccine reduces the risk of genital warts and precursor lesions of cervical, vaginal and vulvar cancers caused by the virus types in the vaccine. It is a prophylactic vaccine — there is no evidence that it treats infection or prevents disease caused by pre-existing HPV infection.<sup>4</sup>

There is no published evidence that the quadrivalent HPV vaccine protects against infection with HPV types not included in the vaccine. The sponsor has recently announced that it has submitted to regulatory authorities data that show protection against other HPV types, but the details are not publicly available.<sup>5</sup>

The vaccine is of most benefit to women with no previous infection with any of the HPV types included in the vaccine, who are most likely to be sexually naïve. Sexually active women who may have had previous HPV infections may also benefit (although possibly to a lesser extent) from protection against infection with HPV types they have not been previously infected with but which are covered by the vaccine.

Women who receive the vaccine must still have regular Pap smears because the vaccine does not protect against

all HPV types that can cause cervical cancer. Cervical cancer can result from persistent infection with an HPV type not covered by the vaccine or because HPV types 16 or 18 were acquired before vaccination.

## The human papillomavirus

Cervical cancer develops only after persistent infection with some types of HPV, although very few infections develop into cancer.

More than 40 types of HPV can infect the genital tract. HPV types can be classified according to their associated risk of cervical cancer. Fifteen high-risk HPV types have been identified. Types 16 and 18 are responsible for 70% to 80% of cervical cancers. HPV is implicated in a range of other cancers: it causes 35% to 50% of vulvar and vaginal cancers, as well as some anal, penile and oropharyngeal cancers.

HPV infection can also cause genital warts. Types 6 and 11 are responsible for more than 90% of genital wart cases and can also cause recurrent respiratory papillomatosis, a very rare condition in which warts or papillomas form in the upper respiratory tract.<sup>6</sup>

Most sexually active women are infected with one or more types of HPV at some point.<sup>7</sup> Infection occurs most frequently between the ages of 15 and 25 years.<sup>8</sup> HPV is transmitted via sexual contact, through the genital skin and mucosa rather than in body fluids. Consistent condom use may reduce the risk of HPV infection<sup>9</sup> but transmission is still possible because condoms do not prevent all genital contact.

More than 90% of HPV infections are cleared spontaneously within 1 year.<sup>7</sup> Most infections are asymptomatic or cause low-grade squamous intra-epithelial lesions, which tend to regress.<sup>8</sup> Persistent infections with high-risk HPV types can develop into high-grade lesions, which usually resolve spontaneously, but a small number may progress to cancer.<sup>8</sup> It usually takes 10–20 years for early cytological changes to develop into cervical cancer.

## Vaccine has greatest benefit for females with no prior exposure to HPV

Four studies in about 20,000 women aged 16–26 years have assessed the efficacy of the quadrivalent HPV vaccine against the development of HPV-related disease.<sup>10–12</sup> Results from the 2 largest studies from a mean follow-up of 3 years were recently published<sup>13,14</sup>;

final results (including an additional 8–9 months of follow-up) are yet to be published. The results presented here are from a pooled analysis of all 4 studies (with a mean follow-up time of 2 years) that was submitted to regulatory agencies.<sup>4,12</sup>

The studies assessed efficacy against invasive cervical cancer caused by the HPV types in the vaccine, using as surrogate markers the obligate precursor lesions cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma in situ (AIS). The incidence of low-grade CIN, genital warts and surrogate markers of vulvar and vaginal cancers were also assessed. Surrogate measures were used because cancer is uncommon and takes a long time to develop (so very large and long studies would be required) and screening allows detection and treatment of high-grade lesions before they progress to cancer, so it would be unethical to allow cases of cancer to occur.<sup>15</sup>

In the per protocol population, the quadrivalent HPV vaccine had 100% efficacy against surrogate markers of cervical cancer caused by HPV types included in the vaccine. This analysis included only women with no evidence of previous or current infection with the virus types included in the vaccine, who received all 3 vaccine doses on schedule and who did not deviate from the trial protocol.<sup>12</sup>

Other analyses demonstrate the vaccine's lower protective efficacy when broader populations and disease outcomes are included. In a subgroup of women with no evidence of previous or current infection with the virus types included in the vaccine the protective efficacy against CIN2/3 or worse associated with *any* HPV type was 38% (95% confidence interval [CI] 13% to 56%).<sup>4</sup> Efficacy in a mixed population of HPV-positive and HPV-negative women was 39% (95% CI 23% to 52%) against CIN2/3 or worse associated with the HPV types included in the vaccine, and 12% (95% CI < 0 to 25%) against outcomes associated with *any* HPV type.<sup>4</sup> These figures are from interim analyses and are likely to underestimate longer-term efficacy in these populations because of the occurrence of disease caused by HPV 16 or 18 infection present before vaccination.<sup>13</sup> However, they demonstrate that cervical cancer can still occur in vaccinated women via pre-vaccination infection with HPV types covered by the vaccine or from infection with high-risk HPV types not included in the vaccine.

Furthermore, the trial results are not directly generalisable to the Australian population of women

who are eligible for the vaccine. Only women aged 16–26 years were included in the trials. Women were excluded if they had had more than 4 sexual partners, a history of genital warts or Pap test abnormality. In addition, the rate of HPV infection and proportion of virgins in the Australian population of this age group may differ from the trial population, almost all of whom were sexually active.

The efficacy of the quadrivalent HPV vaccine against genital warts and surrogate markers of vulvar and vaginal cancers has also been assessed, with a pooled analysis of 3 trials recently published. In women without previous infection the vaccine had 100% protective efficacy against surrogate markers of vulval and vaginal cancers caused by HPV types included in the vaccine. In a mixed population of HPV-positive and HPV-negative women it had 49% protective efficacy (95% CI 18% to 69%) against surrogate markers of vulval and vaginal cancers caused by *any* HPV type.<sup>16</sup>

### Long-term efficacy unknown

From the clinical trial data submitted for regulatory approval, the manufacturer concluded that the protective efficacy of the quadrivalent HPV vaccine is durable for at least 2.5 years.<sup>4</sup>

Five-year follow-up of 241 women from one of the original efficacy trials found no cases of cervical disease or genital warts and 2 cases of persistent HPV infection among those who had been vaccinated, compared with 46 cases of persistent infection and/or disease in the placebo group.<sup>17</sup>

Much longer follow-up of a larger number of women is required to confirm the duration of effect of the vaccine.

The results of Pap tests, cervical biopsies and definitive therapy procedures of almost 6000 women who participated in trials in several Nordic countries will be monitored through national cancer registries to provide more information about the long-term efficacy of the vaccine and indicate whether booster doses are needed.<sup>4</sup>

### Bridging to younger girls

The efficacy of the quadrivalent HPV vaccine against HPV-related disease has not been directly demonstrated in girls younger than 16 years. The proportion of sexually active girls is lower in this age group, so much larger and longer studies would be required to demonstrate efficacy. In addition, there are ethical issues associated

with genital examination and specimen collection in pre-adolescent girls. Equivalent clinical efficacy is expected in this age group because the immune response to the vaccine in girls aged 9–15 years is at least equivalent to the response in the age group included in the clinical efficacy studies.<sup>4,12</sup>

### Cervical screening is still needed

Women should have regular Pap smears even if they have received the HPV vaccine, because:

- the vaccine does not protect against the 30% of cervical cancer cases caused by HPV types other than 16 and 18
- the vaccine does not protect against cervical cancer caused by pre-existing infections with HPV 16 and/or 18
- vaccination may not provide complete protection in all women
- the duration of vaccine protection is unknown.

Pap smears every 2 years can prevent more than 90% of cervical cancers.<sup>18</sup> However, about 40% of Australian women aged 20–69 years do not have regular Pap smears.<sup>19</sup> Simple reminders and advice from a health professional about the importance of regular Pap smears can increase participation in screening.<sup>20</sup> Current recommendations for Pap smear frequency are given in Box 1.

More information, including fact sheets for health professionals and consumers, is available from the National Cervical Screening Program website (Box 1).

### Who will benefit from vaccination?

Females who have had no previous exposure to any of the HPV types included in the quadrivalent HPV vaccine will receive the most benefit from vaccination. Ideally, girls should receive the vaccine before they become sexually active. The ongoing school-based program funded under the NIP will target girls in their first year of secondary school.<sup>1</sup>

Females who are sexually active can receive the quadrivalent HPV vaccine but may receive less benefit from it if they have already been exposed to one or

more of the HPV types included in the vaccine. However, the vaccine will still provide protection against infection and disease caused by other HPV types with which they have not previously been infected but that are covered by the vaccine. The risk of new exposure to other HPV types will largely depend on the woman's number of future sexual partners.

Testing for HPV infection before vaccination is not currently recommended.<sup>22</sup> Commercially available HPV DNA tests require a liquid-based cytology sample and do not specify which HPV type is present. Serological assays for HPV are research tools that are insufficiently sensitive for diagnostic testing and currently are not commercially available.<sup>22</sup>

### Clinical efficacy in males is untested

The quadrivalent HPV vaccine is approved (but not funded under the NIP) for use in boys aged 9–15 years for preventing infection with HPV types 6, 11, 16 and 18.<sup>23</sup> This approval is based on safety and immunogenicity data<sup>4</sup> because the efficacy of the vaccine in preventing HPV-related disease in males is not confirmed, although studies are ongoing.

#### Box 1: Australian recommendations for Pap smear frequency<sup>21</sup>

- All women who have ever been sexually active should start having regular Pap smears at age 18–20, or 1–2 years after first intercourse, whichever is later.
- Women who have no symptoms or history suggestive of abnormal cytology\* should have a Pap smear every 2 years.
- Pap smears may stop at the age of 70 years for women who have had 2 normal Pap smears within the last 5 years. Women over 70 years who have never had a smear or who request one should be screened.

These recommendations apply to all sexually active women, whether they are in heterosexual or same-sex relationships.

\* Revised Australian guidelines for managing asymptomatic women with abnormal Pap smears were implemented in July 2006.<sup>8</sup> See the National Cervical Screening Program website ([www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/hpv](http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/hpv)) for more details.

## Safety issues

Injection-site reactions and mild systemic reactions were the most common adverse effects of the quadrivalent HPV vaccine in clinical trials.

Injection-site reactions, commonly pain, redness and swelling, were reported by 83% of people who received the vaccine, compared with 73% who received a placebo vaccine.<sup>4</sup> Most reactions were mild–moderate; fewer than 5% were classified as severe.<sup>4,12</sup>

Headache and fever were the most common systemic reactions. During the fortnight after vaccination, fever was reported by 13% and 11%, and headache by 26% and 28%, of vaccine and placebo recipients, respectively.<sup>4</sup>

Serious adverse effects were very rare. Of more than 11,000 people who received the vaccine in trials, 5 had serious adverse effects that were judged to be definitely, probably or possibly related to the quadrivalent HPV vaccine. These were bronchospasm (possibly related), gastroenteritis (possibly related), headache plus hypertension (definitely related), injection-site pain plus impairment of joint movement (possibly related) and vaginal haemorrhage, which was initially assessed as probably related but after review was considered to be attributable to a previous condition.<sup>4,24</sup>

The quadrivalent HPV vaccine is contraindicated in people with yeast allergy. The vaccine is manufactured in yeast and so may contain minute amounts of yeast protein.<sup>25</sup>

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

Vaccine-related adverse effects can also be reported to the State/Territory health departments in the Australian Capital Territory, Northern Territory, Queensland, South Australia and Western Australia. ADRAC forwards reports of vaccine-related adverse effects to State/Territory follow-up programs.

## Dosing issues

The quadrivalent HPV vaccine is given intramuscularly in the upper arm or thigh. Appropriate medical treatment should be available when it is administered in case of an anaphylactic reaction.

Three separate doses are required. Ideally, the second dose should be given 2 months after the first, and the third should be given 6 months after the first dose.<sup>23</sup> However, in clinical trials the vaccine was still effective when this schedule was not adhered to but all 3 doses were given within a year. If an alternative vaccination schedule is needed, the second dose should not be given less than 1 month after the first, and the third dose should not be given less than 3 months after the second dose.

As with all vaccines, low-grade fever and mild upper respiratory tract infection are not contraindications to vaccination. It may be prudent to delay vaccination in more severe febrile illness.

Immunosuppression is not a contraindication to vaccination. The vaccine is not dangerous to the immunocompromised (because it does not contain live virus) but may be less effective.<sup>22,26</sup>

The vaccine should not be given to pregnant women because of the lack of data on its safety in this population. If pregnancy occurs after the first or second dose, delay finishing the course until after the pregnancy.<sup>23</sup>

The quadrivalent HPV vaccine may be given at the same time as (but at a different site from) hepatitis B vaccine. Use at the same time as other vaccines has not been investigated.

## Information for patients

Suggest or provide the Gardasil consumer medicine information (CMI) leaflet (available at [www.nps.org.au/consumers](http://www.nps.org.au/consumers)).

Advise women and girls who are vaccinated that:

- the vaccine does not protect against all cervical cancers, so they must have regular Pap smears. Young women should begin cervical screening when they reach the appropriate age (Box 1)
- they should continue to practise safe sex because the vaccine does not prevent other sexually transmitted infections
- adverse effects such as redness and swelling at the injection site and mild fever are common in the days after vaccination.

Females who are sexually active or have had previous HPV-related disease should be advised that the vaccine will not protect them against disease caused by vaccine HPV types with which they have already been infected.<sup>22</sup>

Information for consumers about cervical cancer screening and the link between HPV and cancer is available from the National Cervical Screening Program website (see Box 1).

Information for people with concerns about the safety of vaccines is available from the Immunise Australia Program website ([www.immunise.health.gov.au](http://www.immunise.health.gov.au)) then follow the link to Common questions and answers / Immunisation: myths and realities). A recent *Medical Journal of Australia* article<sup>27</sup> about vaccine constituents may also be helpful for health professionals discussing safety concerns with consumers.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.