

Gardasil: first vaccine for human papillomavirus infection

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PRODUCT PROFILE

Proprietary name: Gardasil

Constituents: human papillomavirus vaccine (types 6, 11, 16, 18), recombinant, adsorbed

Indication: prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) related to HPV types 6, 11, 16 and 18 in females aged 16-26 and in children and adolescents aged 9-15 years



Dosage and method of administration: three separate 0.5ml doses administered at 0, 2 and 6 months; alternately the second dose can be administered at least one month after the first, and the third dose at least three months after the second; all three doses should be given within a one-year period; the need for a booster dose has not been established; 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

Contraindications: hypersensitivity to the active substances or to any of the excipients; individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Gardasil should not receive further doses; administration should be postponed in subjects suffering from an acute severe febrile illness, although the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation

Precautions: appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following administration; as with any vaccine, vaccination with Gardasil may not result in protection in all recipients; will only protect against diseases that are caused by HPV types 6, 11, 16 and 18, and appropriate precautions against sexually transmitted diseases should continue to be used; has not been shown to have a therapeutic effect and the vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulvar and vaginal dysplastic lesions or genital warts; also not intended to prevent progression of other established HPV-related lesions; vaccination is not a substitute for routine cervical screening, and routine screening remains critically important and should follow local recommendations; no data on the use of Gardasil in subjects with impaired immune responsiveness, who may not respond to the vaccine; should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals; duration of protection currently unknown

Pregnancy and lactation: not recommended during pregnancy; can be given to breastfeeding women

Interactions: none

Side-effects: *very common:* pyrexia, at the injection site: erythema, pain, swelling; *common:* at the injection site: bleeding, pruritus

Presentation/cost: prefilled syringe, 0.5ml £80.50

Gardasil is a quadrivalent human papillomavirus vaccine for the prevention of cervical cancer, cervical and vulvar dysplasia and external genital warts. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and Dr Anne Szarewski comments on the implications of the proposed immunisation programme.

Human papillomavirus (HPV) infection is the commonest sexually transmitted disease worldwide, with around half of women infected five years after starting to have sex and a peak incidence between the ages of 16 and 23. Thirteen of the 40 virus subtypes are carcinogenic, causing cancers of the cervix, vulva, vagina and anus; HPV also causes genital warts and juvenile recurrent respiratory papillomatosis.¹

About 2800 cases of cervical cancer and 1000 cases of vulval cancer are diagnosed in the UK annually.^{2,3} HPV subtypes 16 and 18 cause approximately 70 per cent of high-grade cervical dysplasia (cervical intraepithelial neoplasia, CIN 2/3) and adenocarcinoma *in situ* (AIS) cases, 70 per cent of high-grade vulvar dysplasia (vulvar intraepithelial neoplasia, VIN 2/3)

cases in young premenopausal females, and most high-grade squamous vaginal lesions (see Table 1).

CIN 3 is an immediate precursor of invasive cervical cancer, and VIN 3 is a risk factor for vulvar cancer in young premenopausal females infected with carcinogenic HPV types.^{1,4}

HPV subtypes 6, 11, 16 and 18 cause about 35-50 per cent of cases of mild CIN 1, and HPV 16, 18 and 31 are associated with VIN.^{1,4}

HPV 6 and 11 are not associated with cervical or anal cancer but account for 90 per cent of cases of genital warts.^{1,4} In 2001, the rate of diagnosis of genital warts was 680 per 100 000 females.⁵

A vaccine effective against HPV would therefore substantially reduce the incidence of some cancers among women. Its benefits for men are less clear, but as they are the most important vectors for transmission to women they are also a potential target group for vaccination.

The technology

Gardasil is a quadrivalent vaccine comprising virus-like particles (L1 protein) of HPV 6, 11, 16 and 18. It is licensed for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to these HPV subtypes in males and females aged at least nine years.

The vaccine is administered as three intramuscular injections at 0, 2 and 6 months (or alternatively at 0, 1 and 3 months). Seroconversion is achieved in at least 99 per cent of individuals one month after completion of the course and persists for at least five years.⁴ The immunogenicity of the vaccine (defined as levels of anti-HPV antibodies) is significantly greater in

HPV subtype	Condition	Percentage of cases
16, 18	adenocarcinoma high-grade cervical dysplasia high-grade vulval dysplasia high-grade squamous vaginal lesions	70% 70% 70%
6, 11, 16, 18	mild cervical dysplasia	35-50%
6, 11	genital warts	90%
16, 18, 31	vulval intraepithelial neoplasia	

Table 1. Gardasil is active against HPV subtypes 6, 11, 16 and 18

children aged under 12 than in older children or young adults.⁴

Clinical trials

Evidence for efficacy in preventing CIN and external genital lesions (EGL: genital warts, vulvar or vaginal intraepithelial neoplasia or cancer) due to HPV comes from two pivotal, randomised, placebo-controlled trials in women aged 16-23: FUTURE 1^{1,6} (n=5455) and FUTURE 2 (n=12 167).⁷ Pooled analysis of these and two other trials are also available.^{1,8}

FUTURE 1

In FUTURE 1, the primary end-points were the incidences of HPV 6/11/16/18-related CIN (grades 1-3), AIS and cervical cancer, and EGL. Participants were not screened at recruitment and included women who were or were not HPV positive.¹

After two years, the vaccine was 100 per cent effective in preventing EGL events and CIN of all severities among the subgroup of women who were seronegative for HPV and who received all scheduled injections.¹

By intent-to-treat (ITT) analysis (including women who received at least one injection and who may have been HPV positive), overall efficacy against CIN was 43 per cent. Efficacy decreased with

CIN severity from 51 per cent for CIN 1 to 0.2 per cent for CIN 3/AIS. Overall efficacy against EGL was 68 per cent, and 64 per cent specifically against vaginal or vulvar intraepithelial neoplasia grade 2/3.¹

FUTURE 2

The primary end-point in FUTURE 2 was the combined incidence of cervical cancer, CIN 2 or 3, or AIS related to HPV 16 or 18 in the per protocol population (this was preferred to ITT analysis because it excluded women seropositive for HPV-16 or HPV-18; about 20 percent of randomised women were found to be seropositive and are included in the ITT population).⁷ After a mean follow-up of three years, the vaccine was 98 per cent effective in preventing this composite end-point. No cases of cervical cancer occurred in either the placebo or treated groups in women who completed all injections and were HPV negative at baseline.

In the ITT analysis (defined as for FUTURE 1), overall efficacy was 44 per cent (see Figure 1; 57 per cent for CIN 2, 45 per cent for CIN 3 and 28 per cent for AIS).⁷

Other studies

Pooled analysis of both FUTURE studies and two other placebo-

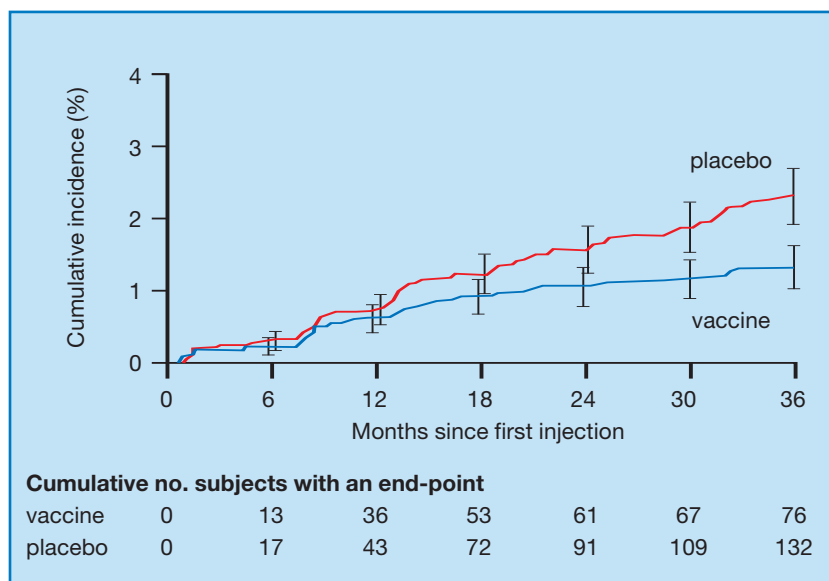


Figure 1. FUTURE 2: cumulative incidence of composite end-point (CIN 2/3 or AIS associated with HPV-16 or HPV-18) showing an overall vaccine efficacy of 44 per cent (after reference 7)

controlled studies, involving a total of 20 583 women, confirmed the vaccine's efficacy against HPV-16 and HPV-18 over a mean follow up of three years.⁸ In a second (unpublished) pooled analysis, the vaccine appeared to be equally effective against all four HPV subtypes¹ and, in women who were positive for one HPV subtype, the vaccine effectively prevents infection by other subtypes.⁴

Five-year follow-up of 241 women at one centre showed that the incidence of HPV infection was reduced by 96 per cent; there were no HPV 6/11/16/18-related CIN or genital warts compared with six cases among placebo recipients.⁹

Adverse effects

The incidence of adverse events in clinical trials was similar for the vaccine and placebo with the exception of moderate (26 vs 18 per cent respectively) and severe (4.5 vs 1.9 per cent) injection-site reactions.¹ There was no evidence of an increased risk of congenital malformations or neonatal complications associated with the vaccine.

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Place in prevention

Each year worldwide an estimated 400 000 women develop cervical cancer and 270 000 die of the disease. Cervical cancer is common between the ages of 30 and 45, thus affecting women with young families. As a result, its combined social, economic

and emotional burden is immeasurable. Genital warts are also a major cause of morbidity: the estimated cost of genital wart treatment in genitourinary medicine clinics in 2003 in the UK was about £23 million.¹

In the UK, the incidence of cervical cancer has dropped substantially since 1988 when the UK national call-recall system began,

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but the diagnosis and treatment of precancerous cervical abnormalities result in significant anxiety.^{2,3} Cervical screening programmes are expensive: the programme in the UK, including the treatment of cervical abnormalities, costs an estimated £150 million per year.⁴ This is beyond the reach of many countries.^{5,6}

Screening tests detect cellular abnormalities early, but this is still only secondary prevention. Since a virus (HPV) is known to be necessary for the development of these cancers, primary prevention with a vaccine is an obvious goal.

In theory, an HPV vaccine could prevent almost all cervical cancer, eventually removing the need for cervical smears. However, until the number of HPV types in the vaccine is increased, there will still be cancers not prevented by vaccination. In addition there is at least one whole generation of women for whom the vaccines have come too late to precede sexual activity and who will continue to require screening.

It is, however, clear that screening programmes, where they exist, will need to adapt when HPV vaccination becomes widespread. How this is done will depend on many factors, including the uptake of the vaccine, the current success of the existing screening pro-

gramme and women's attitudes to attending for cervical smears. A crucial deciding factor will be financial, and this, of course, is subject to the vagaries of politics, public opinion and government priorities.

In the UK, it has recently been announced that, subject to a cost-effectiveness evaluation, the vaccination programme will be directed at 12 and 13-year-old girls, starting not before Autumn 2008.⁷ In the USA, a 'catch-up' programme for girls aged 13-26 years has also been approved, but this is not envisaged in the UK. However, this does not mean that older teenagers and women cannot have the vaccine, but they may have to pay for it.

References

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