Translated from ***Rev Prescrire*** **February 2008; 28 (292): 91**

papillomavirus vaccine types 16 and 18

New Drug

Cervical cancer: just another vaccine

● **The papillomavirus 16, 18 vaccine, like the papillomavirus 6, 11, 16, 18 vaccine, reduces the risk of high-grade cervical dysplasia due to all viral genotypes by about 40% in young women who are not yet infected at the time of vaccination. The vaccine does not seem to provoke any serious adverse effects, but there is no proof that it reduces the risk of cancer.**

NOTHING NEW

Prevention of cervical cancer is based first and foremost on well-organised screening. The papillomavirus 6, 11, 16, 18 vaccine (Gardasil°) reduces the incidence of both high-grade dysplasia (usually associated with genotypes 16 and 18) and anogenital warts (mainly due to genotypes 6 and 11) (1). Protection reaches nearly 100% for high-grade dysplasia due to the genotypes contained in the vaccine. But after 4 years, it is only about 40% for all genotypes.

A few months after the introduction of the papillomavirus 6, 11, 16, 18 vaccine, another vaccine, covering only genotypes 16 and 18 (Cervarix°, GlaxoSmithKline), was announced.

Same limitations in efficacy. One comparative trial versus hepatitis A vaccine included 776 women aged from 15 to 25 who had not yet been infected by one of the 14 viral genotypes with high carcinogenic potential. After 4.5 years of follow-up the frequency of high-grade cervical dysplasia was lower in the papillomavirus vaccine group, with a 95% confidence interval (95% CI%) of -31.9% to 94.3% (2,3).

A double-blind trial involving 18 644 women aged from 15 to 25, compared the papillomavirus 16, 18 vaccine with a hepatitis A vaccine (3-5). After a median of 15 months, among women who were not infected by papillomavirus type 16 or 18 at trial initiation (more than 80% of the women enrolled), two cases of high-grade dysplasia had occurred in the papilloma vaccine group and 21 cases in the control group, representing a statistically significant reduction of 90.4%. The overall reduction (regardless of viral genotype) was -38.2% (95%CI 18.0% to 53.7%; p<0.0001).

In an ongoing double-blind trial, 2189 women aged from 18 to 25, already infected by a papillomavirus, received either the papillomavirus 16, 18 vaccine or a hepatitis A vaccine (6). One year after vaccination, genotype 16 or 18 infection had disappeared in about half of women, with no difference between the groups.

Same adverse effect profile. The adverse effect profile of the 16, 18 vaccine, which mainly includes local reactions, seems similar to that of the 6, 11, 16, 18 vaccine. No serious adverse effects have been reported to date (1,3).

Overall, 1737 pregnancies occurred during or after vaccination with the 16, 18 vaccine in clinical trials (3). No teratogenicity has been reported, but it is better to err on the side of caution and avoid vaccinating pregnant women (3).

In practice: no progress. Data on the papillomavirus 16, 18 vaccine are very similar to those obtained with the papillomavirus 6, 11, 16, 18 vaccine. Therefore, it is better to keep using the four-valent vaccine, which also protects against anogenital warts.

In the meantime, cervical cancer screening must continue, along with campaigns to promote safer sex (condoms, etc.), even for vaccinated women.

human papillomavirus vaccine types 16 and 18

(Cervarix°)

Suspension for IM injection

- **20 µg** of L1 protein from human papillomavirus type 16
- **20 µg** of L1 protein from human papillomavirus type 18, adsorbed to aluminium hydroxide

1 prefilled syringe containing 0.5 ml of suspension + needle

■ **Licensed indication:** *"(…) Prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18".*
[EU marketing authorisation, centralised procedure]

Papillomavirus vaccine

Assessment elsewhere

The papillomavirus 16,18 vaccine is marketed (or shortly to be marketed) in a number of countries. The following extracts are from the conclusions reached by other bulletins independent of the pharmaceutical industry (our translations where necessary).

Arznei-Telegramm (Germany): "*Given the data currently available, it is not possible to judge the utility of this papillomavirus vaccine in the prevention of cervical cancer, or its effect on genotypes not contained in the vaccine. No major differences have emerged between the two available vaccines with respect to clinical utility, immunogenicity or adverse effects*" (1).

Australian Prescriber (Australia): "*The need for booster doses is currently unknown*" (2).

Institut for rationel farmakoterapi (Denmark): "(*…) possible long-term adverse effects are not yet known (…). The Danish pharmacotherapy institute has included the papillomavirus vaccine on the list of vaccines recommended for children*" (3).

1- "Zweiter HPV-Impfstoff Cervarix" *Arznei-Telegramm* 2007; **38** (11): 101-103.
2- "Human papillomavirus vaccine-Cervarix" *Australian Prescriber* 2007; **30** (5): 133-134.
3- "Cervarix (Human Papillomavirusvaccine - HPV 16 og 18" 22 October 2007. www.irf.dk accessed 16 November 2007: 3 pages.

Translated from *Rev Prescrire* **February 2008; 28 (292): 101**

fentanyl patch for stable chronic pain in children

New Indication

Used fentanyl patches should be handled with care

● **Fentanyl patch is an alternative for children who cannot tolerate morphine. Patches should be applied on the back of the upper body trunk.**

In France, fentanyl, an opiate analgesic, is available in the form of transdermal patches under the brand name Durogesic° (Janssen-Cilag) (**a**)(1). These patches were first approved for the management of stable chronic cancer pain in adults. They are now also approved for children aged at least two years (**b**)(2).

This licence extension is based on the results of three unblinded clinical trials including 293 children aged from 2 to 16 years who had chronic pain requiring opiate therapy (66 children aged 2 to 6 years, 100 children aged 6 to 12, and 117 children aged 12 to 16) (2,3). The children had already been treated with an opiate (3). The fentanyl patches were effective in relieving pain. Adverse effects were similar to those seen in adults, mainly consisting of fever, nausea, vomiting, constipation, pruritus and drowsiness (3). In practice, oral morphine (**c**) is the first-choice opiate for the management of intense refractory pain in adults and children with cancer. Fentanyl patches are an alternative for patients who cannot tolerate morphine (1,4).

Special precautions. Several precautions must be taken when using fentanyl patches: they must not be cut into pieces; used patches must be folded and placed in the disposal system provided in the box; and the date of application must be noted. Other precautions apply specifically to children: the patches must only be used after another type of opiate therapy; and they should be applied to the back of the upper body trunk to prevent the child from removing them. (Note that the packet insert shows a diagram with a patch applied to the chest, which is a potential source of confusion).

The patches contain a large amount of fentanyl, even after use: deaths have been reported in children after they played with used patches (5,6).

fentanyl
(Durogesic°)

Patches

■ **New wording for the dose regimen** (supplementary text): *"In children (2 to 16 years): (…) In young children, it is best to apply the patch to the upper back to prevent the child from removing it. (…) Durogesic must only be administered to children aged from 2 to 16 years who tolerate major opioids at stable doses and who are receiving the equivalent of at least 30 mg of oral morphine per day"* (1).

1- Afssaps "RCP-Durogesic 12 µg/h, 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h" 4 April 2007: 55 pages.

a- In France, fentanyl is also available for injection and as lozenges for oral transmucosal administration.

b- Previously, the SPC only included a dose regimen for adults, stating: "the safety and efficacy of transdermal fentanyl has not been established in children" (ref 7).

c- Oral forms of morphine are available for children under 6 and for children who cannot swallow tablets or capsules; they include an oral solution without sweeteners or flavouring (Oramorph°), and a syrup with both sweeteners and flavouring (Morphine Aguettant°) (ref 8). Sustained-release morphine capsules can be opened and their contents mixed with a little food. According to the French SPCs, all these oral forms of morphine can be used in children from the age of 6 months (refs 7,9).

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Fentanyl" *Prescrire Int* 1998; **7** (37): 138-140.
2- Afssaps "RCP-Durogésic + notices" 4 April 2007: 100 pages.
3- Heads of Medicines Agencies "Public assessment report paediatric data - Durogesic" 10 January 2007. www.hma.eu accessed 16 October 2007: 25 pages.
4- "Opioid analgesics" + "Prescribing in palliative care - pain". In: "BNF for children" BMJ Publishing Group, London 2007. www.medicinescomplete.com accessed 15 October 2007: 7 pages.
5- Prescrire Rédaction "Fentanyl: attention !" *Rev Prescrire* 2006; **26** (269): 107.
6- Prescrire Rédaction "Fentanyl transdermique: les risques d'un opiacé" *Rev Prescrire* 2006; **26** (268): 26.
7- French datasheet compendium "Dictionnaire Vidal" Vidal, Issy-les-Moulineaux 2007.
8- Prescrire Rédaction "morphine buvable-Oramorph°" *Rev Prescrire* 2006; **26** (275): 570.
9- Afssaps "RCP-Oramorph" 15 October 2007 + "RCP-Morphine Aguettant" 2 May 2007: 18 pages.

Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Human papillomavirus vaccine for genotypes 6,11,16,18" *Prescrire Int* 2007;**16** (89): 91-94.
2- Harper DM et al. "Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised controlled trial" *Lancet* 2006; **367**: 1247-1255.
3- European Medicines Agency - CHMP "European Public Assessment Report (EPAR) (first published)-Cervarix. Scientific discussion": 56 pages; posted on EMEA website 3 October 2007.
4- Paavonen J et al. "Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial" *Lancet* 2007; **369**: 2161-2170.
5- GlaxoSmithKline "580299/001 (HPV-001) Clinical Study Report Synopsis" February 2006: 15 pages.
6- Hildesheim A et al. "Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection" *JAMA* 2007; **298** (7): 743-753.

In reply to our request for information, GlaxoSmithKline provided us with thorough and relevant documentation.