Second HPV Vaccine Backed for Girls, Women

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — The majority of a federal advisory panel agreed that the data on a recombinant bivalent human papillomavirus vaccine indicate that the vaccine is safe and effective in preventing cervical cancer and certain precancerous or dysplastic lesions caused by HPV types 16 and 18 in girls and women aged 10-25 years.

The FDA's Vaccines and Related Biological Products Advisory Committee, voted 12-1 that the data on the Glaxo-SmithKline Biologicals human papillomavirus bivalent (types 16 and 18) vaccine, recombinant, supported the efficacy of the vaccine for preventing HPV 16/18–related cervical cancer, cervical intraepithelial neoplasia (CIN) 2+, adenocarcinoma in situ (AIS), and CIN1+ in girls and women aged 15-25 years.

In a separate vote, the panel again voted 12-1 that the results of an immunogenicity bridging study from the United Kingdom, which compared immune responses to the vaccine in recipients aged 10-14 years with those of older recipients, supported effectiveness of this same claim in girls aged 10-14 years. There were no efficacy data in the younger age group, but immune responses for HPV 16/18 in the younger girls were similar to those in the older group. If approved, GSK plans to market the vaccine as Cervarix. GSK has proposed that Cervarix be licensed for prevention of cervical cancer (squamous cell cancer and adenocarcinoma, and protection against precancerous or dysplastic lesions and persistent/incident infections), caused by HPV types 16 and 18, in girls and women aged 10-25 years. It is administered in a three-dose schedule at 0, 1, and 6 months.

The majority of the panel also voted that the data supported the safety of the vaccine in girls and women aged 10-25 years but recommended that safety issues, which included spontaneous abortions, be studied further after licensure. In the pivotal study, there was a higher number of spontaneous abortions around the time of vaccination than in the comparison group.

There also was evidence that vaccination was effective in preventing HPV 16/18 CIN2+ in women who had been previously infected with HPV 16/18, according to GSK.

GSK already has a Cervarix pregnancy registry in the United Kingdom and has announced plans to combine that with a registry in the United States pending FDA approval. The company has also announced plans to conduct a postmarketing safety study.

There were more musculoskeletal and neuroinflammatory events with potential autoimmune causes—although rare—among almost 30,000 Cervarix recipients, compared with controls. The three most common adverse events associated with the vaccine were headache, injection site pain, and fever.

The FDA usually follows the recommendations of its advisory panels. HPV 16 and 18 cause most cervical cancers in the United States. The vaccine was approved in May 2007, in Australia and is now licensed in 98 countries.

In the pivotal phase III, randomized, double-blind international study, more than 18,000 girls and women aged 15-25 in the general population received Cervarix or the active control, Havrix, an inactivated hepatitis A vaccine.

Over a mean follow-up of 39 months after the first dose, the vaccine was 93% effective against HPV 16/18 CIN2+ in seronegative subjects. There also was evidence that vaccination was effective in preventing this end point in women who had been previously infected with HPV 16/18, according to GSK.

Merck's quadrivalent HPV vaccine, Gardasil (human papillomavirus [types 6, 11, 16, 18] quadrivalent vaccine, recombinant), is approved for girls and women aged 9-26 years, for preventing cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18 as well as associated precursor lesions and genital warts caused by HPV types 6 and 11. ■

Bausch & Lomb

Besivance™

besifloxacin ophthalmic suspension, 0.6%

Brief Summary: Based on full prescribing information revised April 2009.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

INDICATIONS AND USAGE
Besivance™ (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:
CDC coryneform group G
*Corynebacterium pseudodiphtheriticum**
*Corynebacterium striatum**
Haemophilus influenzae
*Moraxella lacunata**
Staphylococcus aureus
Staphylococcus epidermidis
*Staphylococcus hominis**
*Staphylococcus lugdunensis**
Streptococcus mitis group
Streptococcus oralis
Streptococcus pneumoniae
*Streptococcus salivarius**
*Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once before use.
Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Topical Ophthalmic Use Only
NOT FOR INJECTION INTO THE EYE.
Besivance™ is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
Growth of Resistant Organisms with Prolonged Use
As with other anti-infectives, prolonged use of Besivance™ (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.
Avoidance of Contact Lenses
Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance™.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.
The data described below reflect exposure to Besivance™ in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.
The most frequently reported ocular adverse event was conjunctival redness, reported in approximately 2% of patients.
Other adverse events reported in patients receiving Besivance™ occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean C_{max} in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day (C_{max}, 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).
In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.
Since there are no adequate and well-controlled studies in pregnant women, Besivance™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers
Besifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance™ is administered to a nursing mother.
Pediatric Use
The safety and effectiveness of Besivance™ in infants below one year of age have not been established. The efficacy of Besivance™ in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials *[see 14 CLINICAL STUDIES]*.
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.
Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.
NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.
No *in vitro* mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.
Besifloxacin induced chromosomal aberrations in CHO cells *in vitro* and it was positive in an *in vivo* mouse micronucleus assay at oral doses ≥ 1500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.
PATIENT COUNSELING INFORMATION
Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other source.
Although Besivance™ is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Besivance™ or other antibacterial drugs in the future.
Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance™.
Patients should be advised to thoroughly wash hands prior to using Besivance™.
Patients should be instructed to invert closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated
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U.S. Patent No. 6,685,958
U.S. Patent No. 6,699,492
U.S. Patent No. 5,447,926

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