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, Bisxavance™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Bisxavance™ should not be measured in human milk, although it can be presumed to be excluded in human milk. Caution should be exercised when bisxavance™ is administered to a nursing mother.

Pediatric Use
The safety and effectiveness of Bisxavance™ in infants below one year of age have not been established. The efficacy of Bisxavance™ 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 bisxavance have not been performed.

No in vivo mutagenic activity of bisxavance was observed in an Ames test (up to 3.33 mg/plate) on bacterial tester strains Salmonella typhimurium TA98, TA100, TA1535, TA1537 and Escherichia coli WP2uvrA. However, it was mutagenic to S. typhimurium strain TA102 and E. coli strain WP2uvrA. Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition. Bisxavance induced chromosomal aberrations in CHO cells in vitro and it was positive in an in vitro mouse micronucleus assay at oral doses ≤ 1500 mg/kg.

Bisxavance induce DNA synthesis in hepatocytes cultured from rats given the test compound up to 2000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, bisxavance 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, nose or other source.

Although Bisxavance™ 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 earlier 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 Bisxavance™ or other quinolone antibiotics.

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 Bisxavance™.

Patients should be instructed to invest closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, hold bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated
Tampa, Florida 33637
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U.S. Patent No. 6,465,958
U.S. Patent No. 5,474,926

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Topical Ophthalmic Use Only

CONTRAINDICATIONS

This product is contraindicated in patients who are taking medicines that inhibit cytochrome P450 3A4, P450 1A2, or P450 1A1/2 metabolism.

This product is contraindicated in patients with known hypersensitivity to any component of this product.

This product is contraindicated in patients with a known bacterial conjunctivitis of the ocular surface.

In the first 2 years of life, according to a report.

The cumulative proportion of children with serotype 19A was significantly higher at the age of 12 and 18 months in both the 2-dose and the 2 + 1–dose groups than in the unvaccinated group.

Center Utrecht, the Netherlands, and her associates.

They performed a post hoc analysis of data from a randomized controlled trial in the western Netherlands when PCV7 vacci- cines were first introduced. The 948 study subjects had been randomly assigned to receive PCV7 at ages 2 and 4 months (the 2-dose group), or PCV7 at ages 2, 4, and 11 months (the 2 + 1–dose group), or no PCV7 (the unvaccinated control group). Nasopharyngeal swabs were then obtained at ages 6 to 7, 6, 12, 18, and 24 months to test for the presence of S. pneu- moniae and its susceptibility to antibiotics.

The cumulative proportion of children with serotype 19A was significantly higher at the age of 12 and 18 months in both the 2-dose and 2 + 1–dose groups than in the unvaccinated group, but not at 6 months, the investigators said (JAMA 2010;304:1099-106).

Sixteen percent of those in the 2 + 1–dose group tested positive for serotype 19A acquisition, which was significantly greater than the 9% rate in the control group; 13% of children in the 2-dose group did so, but this was not significantly higher than in the control group.

The study was supported by the Dutch Ministry of Health. Dr. van Gils’ associates reported ties to GlaxoSmithKline, Wyeth/Pfizer, Baxter, and Novartis.

Major Finding: Sixteen percent of those in the 2 + 1–dose group tested positive for new serotype 19A acquisition, which was significantly higher than the 9% rate in the control group; 13% of children in the 2-dose group did so, but this was not significantly higher than in the control group.

Data Source: A post hoc analysis of data from a randomized controlled trial of vaccination in 1,445 children in the western Netherlands.

Disclosures: This study was supported by the Dutch Ministry of Health. Dr. van Gils’ associates reported ties to GlaxoSmithKline, Wyeth/Pfizer, Baxter, and Novartis.

In introducing the heptavalent pneumococcal conjugate vaccine into routine in- fant immunization programs appears to raise the rate of nasopharyngeal acquisition of pneumococcal serotype 19A strains in the first 2 years of life, according to a report. Researchers had noted a rapid increase in the presence of serotype 19A strains, which are often multidrug resistant, soon after the widespread implementation of heptavalent pneumococcal conjugate vaccine (PCV7) immunization in several countries. However, they were unsure of a definite link between the vaccine and the emergence of the serotype because those strains have also increased in some countries without the PCV7 vaccine.

“We now have demonstrated, to our knowledge for the first time, the facilitat- ing role of PCV7 in nasopharyngeal acquisition of serotype 19A. In view of the proven disease potential of serotype 19A, for otitis media and invasive pneumococ- cal disease and its observed association with antibiotic resistance, vaccines of broader coverage including protection against serotype 19A may further aid pneumococcal disease prevention,” said Dr. Elske J.M. van Gils of Wilhelmina Children’s Hospital, University Medical Center