through persistent fomivirsen selection pressure *in vitro*, to isolate a strain of human CMV that was 10-fold less susceptible to fomivirsen inhibition than the parent strain. (Package Insert, Vitravene, 1998; Mulamba *et al.,* 1998). The molecular and genetic basis for fomivirsen resistance was never elucidated; however, there were no sequence changes in the DNA region where fomivirsen binds in the resistant CMV strain (Mulamba *et al.,* 1998). It remains possible that resistant strains may occur *in vivo*, but none has been identified to date.

Fomivirsen was as active against human CMV isolates that were resistant to ganciclovir, foscarnet, and/or cidofovir as it was against wild-type virus (Mulamba *et al*., 1998; Henry *et al*., 2001). This outcome is not surprising because the mechanism of action of fomivirsen is completely different from these DNA polymerase inhibitors.

3. MECHANISM OF DRUG ACTION

Antisense oligonucleotides such as fomivirsen are highly specific and novel therapeutics that are designed to bind to a specific sequence in the target mRNA via Watson-Crick base pairing. Once hybridized to its target, the oligonucleotide then disables or triggers the degradation of the mRNA. Fomivirsen inhibits CMV replication by binding to mRNA transcribed from a critical immediate early gene region (IE2) of CMV; the mRNA-fomivirsen complex triggers degradation of the mRNA, thereby blocking synthesis of these replication-essential IE2 proteins and fully interrupting virus replication. The fomivirsen target sequence is unique to CMV, and fomivirsen does not bind to any known human mRNA.

The mode of action of fomivirsen is consistent with an antisense mechanism, although it is thought there may be a mode of action unrelated to its antisense activity as well (Azad *et al*., 1993; Anderson *et al*., 1996).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Fomivirsen must be administered only by intravitreal injection, and that allows for a much higher drug concentrations at the site of viral replication (retina) than with systemic (intravenous or oral) administration. The standard technique of intravitreal drug injection by an ophthalmologist, for which new guidelines have been established, is always used to deliver fomivirsen (Avery *et al.,* 2014). Care must be taken to avoid technical problems associated with intravitreal therapy (Aiello *et al*., 2004; Jager *et al.,* 2004). Fomivirsen was never investigated for intravenous or oral administration and should not be given by those routes.

Treatment of CMV retinitis with fomivirsen begins with an induction phase, followed by a maintenance phase. In the induction phase, generally two intravitreal injections of fomivirsen (330 μg/0.05 ml) are given 2 weeks apart, followed by a maintenance schedule of a single injection every 4 weeks.

There are no published studies or clinical data supporting dose adjustments of fomivirsen. Although specific doses and dosing regimens were shown to be efficacious in the clinical trials conducted in support of fomivirsen approval (Vitravene Study Group, 2002a; Vitravene Study Group, 2002b; Vitravene Study Group, 2002c), in clinical practice the clinician may find it necessary to consider modifications of the approved label dosing based on the clinical picture and situation of each individual patient. The dosing schedule depends on clinical observation of the CMV retinitis, and the ophthalmologist may elect to continue an induction course until the disease is quiescent. For example, some patients may require up to four weekly doses for induction therapy. In addition, the maintenance scheduling may also be varied, according to the clinical response of the patient or any change in the immune status (e.g. a rise in CD4 counts due to antiretroviral therapy in an HIV-infected patient reducing the activity of CMV retinitis).

4b. Newborn infants and children

There is no experience with fomivirsen in children; presumably it could be used in children, at least, if intravitreal injection could be performed safely in the patient and other CMV antiviral drugs were not controlling the retinitis.

4c. Pregnant and lactating mothers

Animal reproductive studies have not been conducted with fomivirsen, and no studies have been conducted in pregnant women; hence there are no data on whether fomivirsen would cause harm to the fetus or to breastfeeding infants when administered to the woman. However, given that the drug is confined to the eye, its use during pregnancy or breastfeeding could be considered if other options for treating CMV retinitis were not available or successful.

4d. Patients requiring altered dosages

Because fomivirsen is confined to the eye, patients with renal or hepatic disease can be treated at the usual doses without affecting those organs.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

Fomivirsen is injected into the vitreous and is not found in significant quantities outside of the eye. Within the vitreous, bioavailability is 100%.

5b. Drug distribution

The drug is probably found only in the eye. Neither unaltered fomivirsen nor fomivirsen metabolites were detected in