ACICLOVIR

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Aciclovir

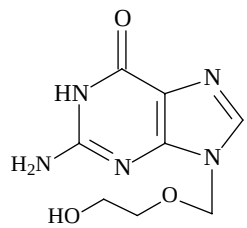
Chem. Abstr. Serv. Reg. No.: 59277-89-3
Chem. Abstr. Name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one
IUPAC Systematic Name: 9-[(2-Hydroxyethoxy)methyl]guanine
Synonyms: ACV; acycloguanosine; acyclovir; BW-248U; 9-(2-hydroxyethoxymethyl)guanine

Aciclovir sodium

Chem. Abstr. Serv. Reg. No.: 69657-51-8
Chem. Abstr. Name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one, sodium salt
IUPAC Systematic Name: 9-[(2-Hydroxyethoxy)methyl]guanine, monosodium salt
Synonyms: Acycloguanosine sodium; acyclovir sodium; acyclovir sodium salt; sodium acyclovir

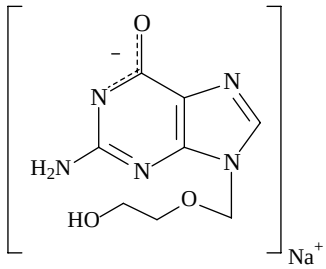
1.1.2 *Structural and molecular formulae and relative molecular mass*

Aciclovir



$C_8H_{11}N_5O_3$ Relative molecular mass: 225.21

Aciclovir sodium



$C_8H_{10}N_5NaO_3$ Relative molecular mass: 247.19

1.1.3 *Chemical and physical properties of the pure substances*

Aciclovir

(*a*) *Description*: White, crystalline powder (American Hospital Formulary Service, 1999)
(*b*) *Melting-point*: 256.5–257 °C (Budavari, 1996)
(*c*) *Spectroscopy data*: Infrared spectral data have been reported (British Pharmacopoeial Commission, 1993).
(*d*) *Solubility*: Slightly soluble in water (1.3 mg/mL at 25 °C); very slightly soluble in ethanol (0.2 mg/mL); soluble in dilute aqueous solutions of alkali hydroxides and mineral acids; freely soluble in dimethyl sulfoxide (American Hospital Formulary Service, 1999; Royal Pharmaceutical Society of Great Britain, 1999)
(*e*) *Dissociation constants*: pK_a, 2.27 and 9.25 (American Hospital Formulary Service, 1999)

Aciclovir sodium

(*a*) *Description*: White, crystalline, lyophilized powder (American Hospital Formulary Service, 1999)
(*b*) *Solubility*: Soluble in water (> 100 mg/mL at 25 °C); but at pH 7.4 and 37 °C, the drug is almost completely un-ionized and has a maximum solubility of 2.5 mg/mL (American Hospital Formulary Service, 1999)

1.1.4 *Technical products and impurities*

Aciclovir is available as 200, 400- and 800-mg tablets, a 200-mg capsule, a 200-mg/5 mL suspension, a 500- or 1000-mg lyophilized powder for intravenous injection, a 50-mg/g (5% w/w) cream in a water-miscible base, a 3% (30 mg/g) ophthalmic ointment in petrolatum and a 5% (50 mg/g) ointment in a polyethylene glycol or soft paraffin base. The tablets may also contain aluminium–magnesium trisilicate, cellulose, copolyvidon, corn starch, FD&C Blue No. 2, hypromellose, indigocarmine, indigotine,

lactose, macrogol, magnesium stearate, methylhydroxypropylcellulose, microcrystalline cellulose, poly(*O*-carboxymethyl)–starch sodium salt, povidone, red iron oxide, silicon dioxide, sodium starch glycolate and titanium dioxide. The capsules may also contain corn starch, lactose, magnesium stearate and sodium lauryl sulfate; the capsule shell may also contain gelatin, FD&C Blue No. 2, one or more parabens and titanium dioxide. The suspension may also contain carboxymethylcellulose sodium, flavours (banana, orange), glycerol, methyl 4-hydroxybenzoate, microcrystalline cellulose, propyl 4-hydroxybenzoate, sorbitol and vanillin. The powder may also contain sodium hydroxide. The cream may also contain cetostearyl alcohol, glycerol monostearate, liquid paraffin, macrogol stearate, petroleum jelly, poloxamer 407, polyoxyethylene fatty acid, propylene glycol, sodium lauryl sulfate and soft white paraffin. Dimeticon was added in the past.

Aciclovir sodium is available as a powder for injection or intravenous infusion in dosages of 25 and 50 mg/mL. After reconstitution with sterile water for injection, aciclovir sodium solutions containing 50 mg/mL aciclovir, have a pH of approximately 11 (10.5–11.7) and are clear and colourless (Gennaro, 1995; American Hospital Formulary Service, 1997; Canadian Pharmaceutical Association, 1997; British Medical Association/Royal Pharmaceutical Society of Great Britain, 1998; Editions du Vidal, 1998; LINFO Läkemedelsinformation AB, 1998; Rote Liste Sekretariat, 1998; Thomas, 1998; Medical Economics Data Production, 1999).

The following impurities are limited by the requirements of the British and European pharmacopoeias: 2-amino-9-{[2-(acetyloxy)ethoxy]methyl]}-1,9-dihydro-6*H*-purin-6-one; 2-amino-1,7-dihydro-6*H*-purin-6-one; 2-amino-7-{[2-hydroxyethoxy]-methyl}-1,7-dihydro-6*H*-purin-6-one; 2-amino-9-{[2-(benzoyloxy)ethoxy]methyl}-1,9-dihydro-6*H*-purin-6-one; 6-amino-9-{[2-hydroxyethoxy]methyl}-1,3-dihydro-2*H*-purin-2-one; 2-acetamido-9-{[2-hydroxyethoxy]methyl}-1,9-dihydro-6*H*-purin-6-one; 2-acetamido-9-{[2-(acetyloxy)ethoxy]methyl}-1,9-dihydro-6*H*-purin-6-one; and 2-acetamido-9-{[2-(benzoyloxy)ethoxy]methyl}-1,9-dihydro-6*H*-purin-6-one (British Pharmacopoeial Commission, 1996; Council of Europe, 1998).

Trade names for aciclovir include Acerpes, Acic, Aciclin, Aciclobene, Aciclobeta, Aciclosina, Aciclostad, Aciclovir, Aciclovir 1A Pharma, Aciclovir AL, Aciclovir Allen, Aciclovir Alonga, Aciclovir-Austropharm, Aciclovir Brahms, Aciclovir Cream BP 1998, Aciclovir Dorom, Aciclovir Ebewe, Aciclovir Eye Ointment BP 1998, Aciclovir Filaxis, Aciclovir Heumann, Aciclovir Oral Suspension BP 1998, Aciclovir NM Pharm, Aciclovir-ratiopharm, Aciclovir-Sanorania, Aciclovir Tablets BP 1998, aciclovir von ct, Acic-Ophtal, Aciklovir, Aciklovir Norcox, Acipen Solutab, Aci-Sanorania, Aciviran Pomata, Aclovir, Activar, Activir, Acyclo-V, Acyclovir, Acyclovir Alpharma, Acyclovir Capsules USP 23, Acyclovir-Cophar, Acyclovir for Injection USP 23, Acyclovir-Mepha, Acyclovir Ointment USP 23, Acyclovir Oral Suspension USP 23, Acyclovir Tablets USP 23, Acyl, Acyrax, Acyvir, Aklovir, Alovir, Antiherpes Creme, Antivir, Apo-Acyclovir, Asiviral, Aviclor, Aviral, Avirase, Avirax, Avix, Avyclor, Avyplus, Awirol, Cevirin, Cicloferon, Cicloviral, Citivir, Clonorax, Cusiviral,

Cyclivex, Cyclovir, Cycloviran, Dravyr, Efriviral, Esavir, Exviral, Geavir, Hermixsofex, Hermocil, Hernovir, Herpesin, Herpetad, Herpex, Herpofug, Herpotern, Herpoviric, Klovireks-L, Lisovyr, Mapox, Maynar, Milavir, Neviran, Nycovir, Orivir, Poviral, Rexan, Sifiviral, Simplex, Soothelip, Supravilab, Supraviran, Virasorb, Virax, Virax-Puren, Virherpes, Virmen, Virocul, Virolex, Virosil, Virovir, Virupos, Viruseen, Xiclovir, Zoliparin, Zoviplus, Zovirax and Zyclir (Royal Pharmaceutical Society of Great Britain, 1999; Swiss Pharmaceutical Society, 1999). Those that have been discontinued include Acicloftal, Aciviran, Clovix, Viclocir, Vipral and Zovir.

Trade names for aciclovir sodium include Acic, Aciclovir Alonga, Aciclovir-Austropharm, Aciclovir Biochemie, Aciclovir Brahms i.v., Aciclovir Ebewe, Aciclovir Filaxis, Aciclovir Genthon, Aciclovir Intravenous Infusion BP 1998, Aciclovir-ratiopharm p.i., Aciclovir-Sanorania, Aciclovir Tyrol Pharma, Acivir, Acyclovir Alpharma, Cicloviral i.v., Cusiviral, Geavir, Herpesin, Herpotern, Heviran, Mapox, Maynar, Nycovir, Supraviran, Supraviran i.v., Virherpes, Virmen, Virolex, Zovir, Zovirax, Zovirax for Injection and Zyclir (Royal Pharmaceutical Society of Great Britain, 1999; Swiss Pharmaceutical Society, 1999). The name Viclovir has been discontinued.

1.1.5 *Analysis*

Several international pharmacopoeias specify infrared absorption spectrophotometry with comparison to standards, thin-layer chromatography and liquid chromatography as the methods for identifying aciclovir; potentiometric titration with perchloric acid and liquid chromatography are used to assay its purity. In pharmaceutical preparations (capsule, cream, eye ointment, intravenous infusion, oral suspension, tablet), aciclovir is identified by ultraviolet absorption spectrophotometry and liquid chromatography; ultraviolet absorption spectrophotometry, ultraviolet fluorescence and liquid chromatography are used to assay for aciclovir content (British Pharmacopoeial Commission, 1993, 1994; US Pharmacopeial Convention, 1994; British Pharmacopoeial Commission, 1996; Council of Europe, 1998; US Pharmacopeial Convention, 1998).

1.2 Production

Aciclovir can be prepared by alkylating guanine with 2-(chloromethoxy)ethyl benzoate and hydrolysing the resulting ester to aciclovir (Gennaro, 1995). Approximately 7.5 tonnes of aciclovir were produced worldwide in 1984 and production has increased significantly since then (Glaxo Wellcome, Inc., 1999).

Information available in 1999 indicated that aciclovir and aciclovir sodium were manufactured and/or formulated in 46 and 22 countries, respectively (CIS Information Services, 1998; Royal Pharmaceutical Society of Great Britain, 1999; Swiss Pharmaceutical Society, 1999).

1.3 Use

Aciclovir and its sodium salt are active against herpes simplex viruses (HSV-1 and HSV-2), varicella-zoster infections, and Epstein-Barr virus. Aciclovir is an acyclic nucleoside analogue, and it is incorporated into viral DNA inside an infected cell where it interferes with viral replication (King, 1988; Gennaro, 1995; see section 4.1 for a more complete description of the mechanism of action of aciclovir).

The first new drug application for aciclovir was filed in 1981, and it was first approved for general systemic clinical use in the United Kingdom and the USA in 1982 (King, 1988). By 1988, aciclovir had been licensed in more than 40 countries, and it was estimated that intravenous and oral preparations had already been used in over 10 million courses of treatment (Tilson, 1988).

Aciclovir is used intravenously in the treatment of severe initial and recurrent mucocutaneous infections caused by HSV-1, HSV-2 and varicella-zoster virus (chickenpox virus) in adults and children. It is also the drug of choice for treatment of herpes simplex encephalitis (American Hospital Formulary Service, 1997; Medical Economics Data Production, 1999).

Aciclovir is frequently given orally in the management of first and recurrent episodes of mucocutaneous herpes in selected patients, for the acute treatment of herpes zoster (shingles) and for the treatment of chickenpox in adults and children. Aciclovir is also used topically in the treatment of mucocutaneous HSV infections, although it is substantially less effective than systemic therapy (American Hospital Formulary Service, 1999).

The oral doses of aciclovir for adults range from 200 mg every 4 h (while awake) to 800 mg three times a day for 5–10 days. For chronic suppression of recurrent infections, the dose is 400 mg twice a day. The oral dose for treatment of chickenpox and herpes zoster is 800 mg aciclovir every 4 h for 5–10 days. Topical treatment of the affected skin or mucous membrane (not conjunctival) with 5% ointment or cream is given up to every 3 h. For ocular herpes simplex keratitis, a 3% ointment may be applied five times daily up to every 4 h until 3 days after healing (Gennaro, 1995; American Hospital Formulary Service, 1999; Royal Pharmaceutical Society of Great Britain, 1999).

In young children, aciclovir is given intravenously at 250–500 mg/m^2 of body-surface area every 8 h. In older children and adults, intravenous injections are given at 5–10 mg/kg bw every 8 h (Thomas, 1998; Royal Pharmaceutical Society of Great Britain, 1999).

Doses of aciclovir should be reduced in patients with renal impairment (American Hospital Formulary Service, 1999; Royal Pharmaceutical Society of Great Britain, 1999).

1.4 Occurrence

Aciclovir is not known to occur as a natural product. No data on occupational exposures were available to the Working Group.

1.5 Regulations and guidelines

Aciclovir is listed in the British, European, French, German, Swiss and US pharmacopoeias (Royal Pharmaceutical Society of Great Britain, 1999; Swiss Pharmaceutical Society, 1999).

2. Studies of Cancer in Humans

Kaplowitz *et al*. (1991) conducted a prospective study of 1146 patients (mean age, 34 years) in 24 treatment centres in the USA who had a history of recurrent genital herpes simplex infection confirmed by culture. The patients were treated with aciclovir at various doses, continously and/or for five-day periods for treatment of episodes of infection. No cancers were reported after a follow-up of three years. In 389 patients who were still under treatment and active surveillance five years after the beginning of the first study, one cancer each of the thyroid, pancreas (resulting in death) and ovary and one malignant melanoma were observed (Goldberg *et al*., 1993). [The Working Group noted that neither the initial study nor the subsequent follow-up was designed to investigate cancer incidence. Thus, the numbers of cancers that were expected were not given, and the relative risk could not be calculated. Furthermore, the low age of the patients, indicating a small expected number of cancers, resulted in poor statistical power to identify an effect. The Working Group also noted the high rate of loss to follow-up.]

In the study of Pluda *et al*. (1990, 1993), described in the monograph on zidovudine, three of eight patients receiving aciclovir plus zidovudine for treatment of symptomatic HIV infection (see IARC, 1996) developed a high-grade, B-cell non-Hodgkin lymphoma. [The Working Group noted that the risk is difficult to interpret in the absence of a suitable reference group consisting of AIDS patients with a similar degree of immunosuppression.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 100 male and 100 female CD-1 Swiss mice [age not specified] were treated with aciclovir [purity not specified] suspended in 0.25% sterile agar at doses of 0, 50, 150 or 450 mg/kg bw by gavage, once daily for 126 (males) and 111 (females) weeks, when the group size was about 20% of that at the beginning of the study. Tissues from control animals and those at the high dose were evaluated histologically. The mean body weights of females at the intermediate and high doses were 2 g higher than those of the control group ($p < 0.01$). Treatment did not affect survival in males, and females at the two higher doses had significantly ($p < 0.05$, log-rank test) longer survival rates than controls. The incidences of benign and malignant tumours were not increased (Tucker *et al.*, 1983a). [The Working Group noted that data on specific tumour incidences were not reported].

3.1.2 *Rat*

Groups of 85 male and 85 female Sprague-Dawley rats [age not specified] were treated with aciclovir [purity not specified] suspended in 0.25% sterile agar at doses of 0 (control), 50, 150 or 450 mg/kg bw by gavage once daily for 110 (males) and 122 (females) weeks, when the group size was about 20% of that at the beginning of the study. Tissues from control animals and those at the high dose were evaluated by microscopy. Ten male and 10 female rats from each group were killed at 30 and 52 weeks. Treatment did not affect survival rates, except that of females at the intermediate dose, which was significantly shorter than that of control females ($p < 0.05$, log-rank test). No increase in the incidence of benign or malignant tumours was observed (Tucker *et al.*, 1983a). [The Working Group noted that data on specific tumour incidences were not reported.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

Aciclovir is active against viruses by virtue of its phosphorylation, incorporation into DNA and the consequent chain termination (Brigden & Whiteman, 1983; Elion, 1983; Laskin, 1984). This series of events occurs readily in herpesvirus-infected tissues but poorly in normal tissues, since the initial phosphorylation is accomplished mainly by a herpesvirus-specific deoxynucleoside (thymidine) kinase (Elion, 1983; Laskin, 1984; King, 1988). Subsequent phosphorylations, to form the aciclovir di- and tri-

phosphates, occur through the action of host cellular enzymes (King, 1988). The aciclovir triphosphate is formed readily and is more persistent than the parent compound, remaining for several hours in cultured cells. The viral polymerase is capable of incorporating aciclovir triphosphate into the growing DNA chain but becomes trapped when attempting to extend the chain with an additional nucleotide, because it is unable to separate from the replication complex (Elion, 1993). Therefore, aciclovir is effective not only because it becomes incorporated into DNA but also because it traps the viral DNA polymerase. The drug is primarily effective for the treatment of HSV-1 and -2 and is less effective against varicella-zoster and Epstein-Barr viruses (Gnann *et al*., 1983; King, 1988).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The absorption, distribution, metabolism and excretion of aciclovir in adults have been reviewed extensively (Laskin, 1983; de Miranda & Blum, 1983; Rogers & Fowle, 1983; Brigden & Whiteman, 1985; O'Brien & Campoli-Richards, 1989; Vergin *et al*., 1995). When taken orally, the drug is poorly absorbed from the gastrointestinal tract, with a reported bioavailability of 15–30%, owing to its limited solubility in an aqueous environment; therefore, intravenous dosing is considered more effective (O'Brien & Campoli-Richards, 1989). The drug is widely distributed throughout the body and has been found in plasma, kidney, lung, liver, heart, vagina, brain, cerebrospinal fluid, aqueous humor, saliva and skin (Laskin, 1983; de Miranda & Blum, 1983; Rogers & Fowle, 1983; Brigden & Whiteman, 1985; O'Brien & Campoli-Richards, 1989; Vergin *et al*., 1995). After oral doses of 200 mg taken four to five times daily or 400 mg taken two to three times daily, the peak plasma concentration is about 2 μmol/L (0.49 μg/mL) (Brigden & Whiteman, 1983). After oral administration, the amount of aciclovir in the kidney and lung was actually higher than that in plasma, while the concentration in cerebrospinal fluid was half of that in plasma (Blum *et al*., 1982; O'Brien & Campoli-Richards, 1989) and the concentration in tear fluid reached 18% of that in plasma (O'Brien & Campoli-Richards, 1989). After topical administration, the epidermal concentration of aciclovir was enhanced 48-fold over that observed after oral dosing, but the delivery of the drug to viruses replicating in the basal epidermis was considerably less efficient (Parry *et al*., 1992).

The pharmacokinetics of intravenously administered aciclovir has been described best by a two-compartment open model (Laskin, 1983; Rogers & Fowle, 1983; O'Brien & Campoli-Richards, 1989). The binding of aciclovir to plasma protein has been reported to be 9–33%; the peak concentrations in plasma are typically achieved within 1.5–3.2 h, and the half-time for drug removal from plasma is about 3 h (Laskin, 1983; de Miranda & Blum, 1983; Rogers & Fowle, 1983; O'Brien & Campoli-

Richards, 1989; Vergin *et al*., 1995). The pharmacokinetics is stable over a wide dose range (Rogers & Fowle, 1983).

After intravenous dosing with aciclovir, 45–75% of the drug is excreted in the urine as unchanged compound, but after oral dosing this percentage is reduced to 14–22%, with a large fraction appearing in the faeces (Laskin, 1983; de Miranda & Blum, 1983; Vergin *et al*., 1995). Two minor urinary metabolites, 9-carboxymethoxymethylguanine and 8-hydroxy-9-(2-hydroxyethyl)guanine, have been reported to constitute 8–14% and about 0.2% of the total dose, respectively (de Miranda & Blum, 1983; Rogers & Fowle, 1983; Brigden & Whiteman, 1985; O'Brien & Campoli-Richards, 1989; Vergin *et al*., 1995). Active renal clearance occurs by glomerular filtration and renal tubular secretion, with a half-time of 2–3 h (Laskin, 1983; O'Brien & Campoli-Richards, 1989) and a clearance rate of 3.8–4.9 mL/min per kg of body weight (Rosenberry *et al*., 1982). In patients with renal impairment, the mean elimination half-time can be extended to 20 h, and the total body clearance rate can be decreased 10-fold; it is therefore necessary to reduce the dose accordingly (de Miranda & Blum, 1983; Rogers & Fowle, 1983; Brigden & Whiteman, 1985; O'Brien & Campoli-Richards, 1989).

Transplacental pharmacokinetics

A 39-year-old pregnant woman, presumed to be at 30 weeks of gestation, was treated with aciclovir (350 mg, or 15 mg/kg bw) intravenously every 8 h throughout the remainder of gestation. At 38–53 h after the last dose, aciclovir was found at a concentration of 0.2–2.8 μg/mL in the urine of the infant, delivered by caesarean section (Greffe *et al*., 1986).

Beginning at week 38 of gestation and continuing until delivery, seven women were treated orally with 200 mg aciclovir every 8 h and eight with 400 mg aciclovir every 8 h. With 200 mg aciclovir, the maternal plasma concentrations at delivery were 0.65–3.5 μmol/L, and the cord plasma concentrations were 0.59–2.2 μmol/L. The maternal:cord plasma ratio ranged from 1.1 to 1.9. With 400 mg aciclovir, the maternal plasma concentrations at delivery were 0–4.1 μmol/L, the cord plasma concentrations were 0–3.4 μmol/L, and the maternal:cord plasma ratio ranged from 0.83 to 1.4. No adverse effects were reported in the newborn infants (Frenkel *et al*., 1991).

4.1.2 *Experimental systems*

The absorption, distribution, metabolism and excretion of aciclovir have been determined in several species. The drug appears to be taken up efficiently by many tissues, including the brain and skin (de Miranda *et al*., 1982; Good *et al*., 1983; Rogers & Fowle, 1983; Fujioka *et al*., 1991; Bando *et al*., 1997). The proportion of drug excreted unchanged in the urine is 3.7% for monkeys, 19% for rats, 43% for mice and 75% for dogs (de Miranda *et al*., 1982). The major urinary metabolite,

9-carboxymethoxymethylguanine, comprised about 5% of the excreted dose in rats, mice and dogs and about 40% in rabbits, guinea-pigs and rhesus monkeys. Like humans, dogs, rats and rhesus monkeys show a biphasic decline in the plasma concentration of aciclovir, indicating a two-compartment open model, with a half-time of 1–3 h (de Miranda *et al*., 1982; Gnann *et al*., 1983).

Rats aged 1–8 weeks received aciclovir by gavage at a dose of 20 mg/kg bw. Gastrointestinal absorption was poor in the 8-week-old rats, with a bioavailability of 7.3%, while rats aged 1–3 weeks had greater intestinal membrane permeability and higher drug bioavailability. Absorption of aciclovir in the gastrointestinal tracts of the young rats was shown to occur by an efficient passive diffusion process, which apparently becomes inefficient at the time of weaning (Fujioka *et al.*, 1991).

Beagle dogs given 20 mg/kg bw aciclovir had a mean peak plasma concentration of 42 μmol/L (10 mg/L) by 1.3–2.2 h, and 30% of the dose was bound to plasma. The mean plasma clearance time was 2.4 h, and 75% of the dose was recovered in urine. The body clearance was similar to the glomerular filtration rate, indicating the absence of active tubular secretion (de Miranda *et al*., 1982).

As HSV lesions are primarily external (mouth, genitals), transdermal administration of aciclovir was studied *in vivo* and *in vitro* in Wistar rats. Skin absorption occurred by a first-order process which resulted in excretion of about 0.24% of the administered drug in the urine as parent drug; no metabolites were found (Bando *et al.*, 1997).

4.2 Toxic effects

4.2.1 *Humans*

A summary of the safety of aciclovir, compiled from case reports (about 20 million individuals) and epidemiological studies (about 50 000 patients) during the first 10 years of its use demonstrated that it rarely has adverse effects in healthy individuals. In the USA, 923 adverse events were reported among > 10 million persons, and 129 of these were classified as serious (Tilson *et al*., 1993). When aciclovir is given orally, the doses are typically low and serious adverse events are extremely rare (Goldberg *et al*., 1986; Mertz *et al*., 1988); however, it is given at higher doses intravenously to individuals with serious illnesses, and is associated with more frequent toxic effects (Tilson *et al*., 1993). The commonest adverse effects include nausea (2.7–8%), vomiting (2.5%), diarrhoea (1.5–2.4%), inflammation at the injection site (9%) and headache (0.6–5.9%) (Ernst & Franey, 1998). The commonest serious effects are neurotoxicity (Adair *et al*., 1994) and nephrotoxicity (Whitley *et al*., 1990).

(*a*) *Neurotoxicity*

Intravenous dosing with aciclovir is commonly associated with neurotoxicity in renally compromised patients, since the drug clearance rates are considerably reduced

under such conditions (Rashiq *et al*., 1993; Tilson *et al*., 1993; Adair *et al*., 1994; Kitching *et al*., 1997). Oral dosing is less frequently neurotoxic but was reported to induce acute disorientation in four patients, three of whom had renal insufficiency (MacDiarmaid-Gordon *et al*., 1992). Renal dysfunction is not an absolute requirement for aciclovir-induced neurotoxicity; but, apart from age and neurotoxic medications (Rashiq *et al*., 1993), other definite predisposing factors have not been defined (Ernst & Franey, 1998). The neurotoxicity induced by aciclovir manifests primarily as tremor (28–30%), myclonus (30%), confusion (30–43%), lethargy (17–30%), agitation (27–33%) and hallucination (20–26%) (Rashiq *et al*., 1993; Ernst & Franey, 1998). Less frequent manifestations (3–17%) include dysarthia, asterixis, ataxia, hemiparesthaesia and seizures (Ernst & Franey, 1998). Neurotoxicity typically occurs during the first 24–72 h of drug administration, and discontinuation of the drug results in a complete return to normal by about 15 days (Rashiq *et al*., 1993; Ernst & Franey, 1998). Haemodialysis has been shown to attenuate aciclovir-induced neurotoxicity effectively in symptomatic patients (Krieble *et al*., 1993; Adair *et al*., 1994).

(*b*) *Nephrotoxicity*

Intravenous infusion of large doses of aciclovir can occasionally cause crystallization of the drug in the renal tubules (Peterslund *et al*., 1988) and, rarely, tubular necrosis (Whitley *et al*., 1990). In patients receiving high doses of aciclovir, reversible increases in serum creatinine concentrations can occur (Kumor *et al*., 1988; Whitley *et al*., 1990; Becker & Schulman, 1996). The existence of compromised renal function, use of other nephrotoxic drugs, rapid infusion of large doses, advanced age and dehydration can all contribute to aciclovir-induced nephrotoxicity (Rosenberry *et al*., 1982; Becker & Schulman, 1996). Like aciclovir-induced neurotoxicity, the nephrotoxic effects are typically transient and rapidly ameliorated by haemodialysis (Whitley *et al*., 1990; Krieble *et al*., 1993; Adair *et al*., 1994; Johnson *et al*., 1994; Vachvanichsanong *et al*., 1995).

(*c*) *Other toxic effects*

Rare effects of intravenous and oral treatment with aciclovir include colitis (Wardle *et al*., 1997) and reversible, mild abnormalities of haematological and clinical chemical parameters (Mindel *et al*., 1988; Goldberg *et al*., 1993). Topical administration may be associated with pain, burning or rash (Rosenberry *et al*., 1982; Gnann *et al*., 1983).

Aciclovir, like other anti-HIV nucleoside analogues, has been associated with a rare (1 in 10^5 to 1 in 10^6 patients) idiosyncratic syndrome of a progressive increase in the activity of liver enzymes in serum, fulminating hepatic steatosis and lactic acidosis. Failure to discontinue the drug can lead to death (US Food and Drug Administration Antiviral Advisory Committee, 1993).

4.2.2 *Experimental systems*

(*a*) *Rodents*

Aciclovir is relatively non-toxic in rodents. The main effect observed is related to kidney function but is dependent on dose, animal strain and route of administration. Wistar rats given three subcutaneous injections of 15 mg/kg bw aciclovir per day for five days (a total of 45 mg/kg bw per day) showed no significant changes (Hannemann *et al*., 1997), but intraperitoneal injection of 100 mg/kg bw aciclovir daily for seven days caused polyuria, increased blood urea nitrogen concentration and fractional excretion of sodium and potassium, suggesting damage to the renal proximal tubules (Campos *et al*., 1992). Obstructive nephropathy, caused by crystalline precipitation of the drug in the renal tubules and collecting ducts, was observed in Long-Evans rats given intravenous injections of 20, 40 or 80 mg/kg bw aciclovir daily for three weeks. These changes were accompanied by increased water consumption, urine output, blood urea nitrogen concentration and kidney weight (Tucker *et al*., 1983b). All of the nephrotoxic effects of aciclovir resolved within two weeks after drug discontinuation. In Sprague-Dawley rats given 50, 150 or 450 mg/kg bw aciclovir per day by gavage for 25 months, no treatment-related toxic effects were observed (Tucker *et al*., 1983a). Taken together, these studies suggest that nephrotoxicity is much more likely to result from intravenous than from oral dosing with aciclovir. Parallel clinical observations support the notion that oral dosing is less toxic than intravenous infusion in humans.

No signs of toxicity were observed in CD-1 mice given aciclovir by gavage at a dose of 50, 150 or 450 mg/kg bw per day for one month (Tucker *et al*., 1983b) or in Swiss mice treated identically for 15 months (Tucker *et al*., 1983a).

(*b*) *Dogs*

As in rodents, high doses of aciclovir given to dogs by infusion over a short time were more nephrotoxic than lower doses given over a longer time. Beagle dogs given rapid intravenous injections of 10, 20, 25, 50 or 100 mg/kg bw aciclovir twice a day for one month showed marked dose-related toxic effects, including death, at the two higher doses. At doses of 20–50 mg/kg bw, decreased ability to concentrate urine, increased blood urea nitrogen concentration and renal tubular damage were observed (Tucker *et al*., 1983b).

Labrador retrievers infused with 210 mg/kg bw/day aciclovir via constant infusion for 43 h and with 15 mg/kg bw aciclovir three times daily for 28 days had significantly decreased glomerular filtration rates and urine concentrating capacity at the higher dose. The authors concluded that continuous infusion of the high dose of aciclovir was more detrimental than intermittent administration of the lower dose (Kimes *et al.*, 1989).

In a one-year study of toxicity, aciclovir was given orally to beagle dogs at a dose of 15, 45 or 150 mg/kg bw per day. Because of vomiting, diarrhoea and weight loss, the two higher doses were reduced to 60 and 30 mg/kg bw early in the study. The only

other reported toxic effects were sore paws due to erosion of the footpads and splitting of the nails at the two higher doses (Tucker *et al.*, 1983a).

(*c*) *Other species*

Ophthalmic and cutaneous testing of aciclovir in guinea-pigs and rabbits preceded topical application and ophthalmic use in patients. Ointments containing 5 and 10% aciclovir were tested on shaved, abraded or intact skin of guinea-pigs for 24 days with no sign of dermal toxicity. In New Zealand white rabbits, corneal applications of 1 and 3% aciclovir in petrolatum ointment for 21 days had no effect, whereas ointments containing 5 and 6% aciclovir produced mild conjunctival irritation when applied to the eyes (Tucker *et al.*, 1983c).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

The Acyclovir in Pregnancy Registry was established to gather data on prenatal exposure to aciclovir between 1 June 1984 and 30 June 1990 and comprised information on 312 women exposed to aciclovir and on their children. Most of the women (> 81%) had taken aciclovir orally at doses of 200–1000 mg per day (3.3–17 mg/kg bw assuming a body weight of 60 kg) for 1 to 39 days during pregnancy. No increase in the number of birth defects was found when compared with that expected in the general population (Andrews *et al.*, 1992). [The Working Group noted that the cases accumulated to 30 June 1990 represent a sample of insufficient size for a reliable conclusion about the safety of aciclovir for pregnant women and their developing fetuses.]

4.3.2 *Experimental systems*

In a two-generation study of reproduction and fertility, groups of 15 mature male and 15 female CD-1 mice were treated once each day by gavage with a 0.25% agar vehicle containing 0, 50, 150 or 450 mg/kg bw aciclovir, beginning 64 days before mating for males and 15 days before mating for females and continuing until day 13 of gestation or through day 21 of lactation. No treatment-related alterations in fertility indices, weight gain, pup survival or body weight were reported for the F_0, F_1 or F_2 generation [no data shown] (Moore *et al.*, 1983).

Groups of 21–27 pregnant Sprague-Dawley rats were treated subcutaneously with a 0.9% saline vehicle containing 0, 12, 25 or 50 mg/kg bw per day aciclovir on days 6–15 of gestation. No signs of maternal or fetal toxicity were reported. The mean concentration of aciclovir in fetal homogenate was dose-related: 0, 0.70, 0.96 and 1.95 μg/g wet weight at the four doses, respectively (Moore *et al.*, 1983).

Nineteen pregnant Wistar rats were treated subcutaneously with three doses of 100 mg/kg bw aciclovir on day 10 of gestation, given at 7:00, 12:00 and 17:00 h. Nine control pregnant rats were treated with the vehicle (0.1 mol/L NaCl) only. Maternal weight gain was reduced by aciclovir during pregnancy, but this was attributed to reduced gravid uterine weight and not to maternal toxicity. Various reproductive and developmental effects were reported in the aciclovir-treated group, including an increased rate of resorptions to implantations, skull anomalies and gross structural anomalies of the vertebral column and tail (Chahoud *et al*., 1988). [The Working Group noted that limited statistical analysis was reported and only one dose was tested.]

Pregnant Wistar rats were treated subcutaneously at 7:00, 12:00 and/or 17:00 h on day 10 or on days 9, 10 and 11 of gestation with either 50, 100 or 200 mg/kg bw aciclovir. On day 11.5 of gestation, the dams were killed and the embryos were evaluated. Dose-related reductions in embryonic growth and increased incidences of abnormalities were observed at the higher doses and with the larger number of doses. Maternal plasma concentrations of aciclovir > 19 mg/mL were associated with embryonic effects (Stahlmann *et al*., 1988). [The Working Group noted that the number of pregnant dams was not defined but probably ranged from 3 to 10 litters.]

Pregnant Wistar rats were treated subcutaneously with a single dose of 100 mg/kg bw aciclovir or three doses of 100 mg/kg bw at 7:00, 12:00 and 17:00 h on day 10 of gestation and were allowed to deliver their pups. At 12 weeks, both groups of male offspring exposed *in utero* had reduced body weight, liver weight (high dose only) and reduced thymus weight and increased spleen weight. The only significant change in organ weights in female offspring was reduced relative (to body weight) weight of the liver. Aciclovir-exposed offspring showed an impaired immune response, as judged from host resistance to *Trichinella spiratis* and immunoglobulin titres (Stahlmann *et al*., 1992). [The Working Group noted that the number of dams exposed per group in the test for immune response was not clear.]

Twelve pregnant EPM-I Wistar rats were treated subcutaneously with saline or 60 mg/kg bw aciclovir on days 1–20 of gestation and were killed on day 20. Treatment severely reduced the weight gain of the dams throughout gestation, increased the ratio of resorptions to implantations and decreased the number of viable fetuses (Mamede *et al*., 1995).

Pregnant New Zealand white rabbits were treated subcutaneously with a 0.9% saline vehicle containing 0, 12, 25 or 50 mg/kg bw aciclovir on days 6–18 of gestation. Five to seven samples of fetal homogenate collected on day 18 of gestation showed mean concentrations of aciclovir of 0, 0.16, 0.21 and 0.32 μg/g at the four doses, respectively. No signs of maternal or fetal toxicity were reported in the fetuses on day 18 or in samples collected on day 29 of gestation from 15–18 additional dams (Moore *et al*., 1983).

Fertilized eggs ($n = 37–47$) from white Leghorn chickens were incubated at 37.5 ± 0.5 °C and the yolk sac was dosed with 30–1000 μg aciclovir or the 0.01 N sodium hydroxide vehicle as a single dose before and after 24 h of incubation. In

another experiment, the embryos in 37–39 fertilized eggs were dosed directly with 3–100 μg aciclovir or 0.01 N sodium hydroxide after two, three or four days of incubation. At evaluation on day 8 of incubation, a dose-related increase in the rate of abnormal development was reported in both series (Heinrich-Hirsch & Neubert, 1991).

Male and female rat embryos collected from pregnant Wistar rats on day 9.5 of gestation were cultured for 48 h in 10–200 μmol/L (2.2–45 μg/mL) aciclovir. Retarded development of the ear anlagen was observed at 25 μmol/L aciclovir, and gross structural abnormalities, especially in the brain, were found at concentrations ≥ 50 μmol/L. Aciclovir at 100 μmol/L resulted in major deformities of the telencephalon and ventricles. No alterations were observed in mouse limb bud explants taken from 11-day-old mouse embryos and exposed to aciclovir at concentrations ≤ 500 μmol/L (Klug *et al*., 1985).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Studies of the genotoxicity of aciclovir have yielded largely negative results, and high concentrations of the compound were generally required to produce a positive result or to induce sufficient cytotoxicity to make a negative result valid (Table 1). The genotoxic effects of aciclovir are related primarily to its clastogenicity. Clive *et al*. (1983) provided a review of the genetic activity profile of this drug.

Aciclovir was not genotoxic in various prokaryotic and lower eukaryotic systems. It did not induce reverse mutation in *Salmonella typhimurium* at concentrations of 0.1 μg to 300 mg/plate, with or without exogenous metabolic activation, in a modified plate assay and in the preincubation assay, with five standard strains of *S. typhimurium*. There was no evidence of differential or absolute killing in the *Escherichia coli pol*A$^+$/*pol*A$^-$ repair assay by aciclovir at concentrations up to 10 mg per well, with or without exogenous metabolic activation. Clive *et al*. (1983) noted that strict proof that aciclovir does not induce *pol*A-repairable DNA damage is lacking, but no evidence of lethal damage was found. Aciclovir did not induce gene conversion in *Saccharomyces cerevisiae* strain D5 over the standard dose range in the presence or absence of exogenous activation.

In cultured mammalian cells, aciclovir was not mutagenic at the *Oua* or *Hprt* locus of mouse lymphoma L5178Y cells or at the *Oua*, *Hprt* or *Aprt* locus of Chinese hamster ovary cells, but it was mutagenic in the *Tk* gene of lymphoma cells and this effect was unambiguous, reproducible and dose-related at concentrations ≥ 400 μg/mL. The occurrence of primarily small-type *Tk* mutant colonies in aciclovir-

Table 1. Genetic and related effects of aciclovir

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli pol A/W3110-P3478, differential toxicity (spot test)	–	–	10 000 µg/plate	Clive *et al*. (1983)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–	–	300 mg/plate	Clive *et al*. (1983)
Sacchromyces cerevisiae, gene conversion	–	–	500 µg/plate	Clive *et al*. (1983)
Gene mutation, Chinese hamster ovary cells *in vitro*, *Hprt* locus	–	–	3000	Clive *et al*. (1983)
Gene mutation, Chinese hamster ovary cells *in vitro*, *Aprt* locus	–	–	3000	Clive *et al*. (1983)
Gene mutation, Chinese hamster ovary cells *in vitro*, *Oua* locus	–	–	3000	Clive *et al*. (1983)
Gene mutation, Chinese hamster ovary cells *in vitro*, *Hprt* locus	–	NT	22.5	Pizer *et al*. (1987)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	+	400	Clive *et al*. (1983)
Gene mutation, mouse lymphoma L5178Y cells, *Hprt* locus *in vitro*	–	–	2400	Clive *et al*. (1983)
Gene mutation, mouse lymphoma L5178Y cells, *Oua* locus *in vitro*	–	–	2400	Clive *et al*. (1983)
Sister chromatid exchange, Chinese hamster cells *in vitro*	(+)	NT	90	Thust *et al*. (1996)
Chromosomal aberrations, Chinese hamster cells *in vitro*	(+)	NT	135	Thust *et al*. (1996)
Cell transformation, BALB/c 3T3 mouse cells	+	NT	50	Clive *et al*. (1983)
Cell transformation, C3H 10T1/2 mouse cells	–	NT	64	Clive *et al*. (1983)
Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	200	De Clercq & Cassiman (1986)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	250	Clive *et al*. (1983)
Micronucleus formation, mouse cells *in vivo*	+		122 iv × 2	Haynes *et al*. (1996)
Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		100 iv × 1	Clive *et al*. (1983)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, Chinese hamster bone-marrow cells *in vivo*	+		500 ip × 1	Clive *et al*. (1983)
Dominant lethal mutation, mice	–		50 ip × 5	Clive *et al*. (1983)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; d, day; iv, intravenous; ip, intraperitoneal

treated lymphoma cells is consistent with a clastogenic response associated with DNA chain termination.

Aciclovir was found to transform BALB/c-3T3 cells at the highest dose tested (50 μg/mL) applied for 72 h, but did not transform similarly exposed C3H/10T1/2 cells. The apparent discrepancy between the two systems may be ascribed in part to the fact that the C3H cells were exposed for shorter times and few cells were used. An effort to normalize these factors between the two assays suggests that the results with the BALB/c cells would have paralleled those of the C3H cells had the exposures been identical [no reason was given for the use of different conditions] (Clive *et al*., 1983).

Aciclovir is clastogenic in mammalian cells both *in vitro* and *in vivo*. Chinese hamster strain V79-E cells were evaluated for the frequencies of sister chromatid exchange and chromosomal aberrations after exposure to 0.0073–2.0 mmol/L of aciclovir and judged to show borderline increases in the frequency of chromosomal aberrations. The authors (Thust *et al*., 1996) did not perform a statistical analysis of these results but used a doubling of the background frequency to assign significance to changes in the frequency of chromosomal aberrations. This fact is important because the increase in chromosomal aberration frequency was due to chromatid gaps and chromatid breaks [although the authors did not discuss these findings]. Exposure of cultured human lymphocytes to 250 and 500 μg/mL aciclovir in the absence of exogenous metabolic activation caused a linear increase in the frequency of chromosomal aberrations, due mainly to chromatid breaks. [The Working Group considered the borderline increase in frequency and the nature of the chromosomal aberrations observed to indicate the clastogenicity of aciclovir at high doses.]

Male CD-1 mice were given two intravenous doses of aciclovir at 0 and 24 h and the frequencies of micronucleated polychromatic erythrocytes were evaluated 48 h after exposure. The frequency of micronucleated cells increased in a dose-related fashion.

When groups of four female and four male CD rats were given intravenous doses of aciclovir up to and including the maximum tolerated dose of 100 mg/kg bw, no increase in the frequency of chromosomal aberrations in bone marrow was found in either sex at any of three sacrifice times. A single intravenous dose of 80 mg/kg bw resulted in a peak plasma concentration of 87 ± 16 μg/mL, however, which is lower than the concentration that caused clastogenic effects in assays for chromosomal aberrations *in vitro*.

In groups of three female Chinese hamsters, intraperitoneal injections of ≤ 100 mg/kg bw aciclovir had no effect, while 500 mg/kg bw caused a very high frequency of chromosomal aberrations 24 h after exposure. For example, one treated hamster had chromosome breaks in 99 of 108 cells scored, and 97 of these 99 breaks occurred at the centromere of a single one of the six intermediate size metacentric chromosomes. The mean concentration of aciclovir in human plasma is 0.2 μg/mL after topical administration, 1.0 μg/mL after intravenous administration and 0.6 μg/mL after oral administration, while the peak plasma concentration found after intraperitoneal administration of 500 mg/kg bw to Chinese hamsters was 611 ± 91 μg/mL, which is

well above the minimum required to cause a clastogenic effect *in vitro.* The authors (Clive *et al*., 1983) noted that the natural bases and their nucleosides are clastogenic at a concentration of about 1 mmol/L and that the clastogenicity of aciclovir in hamsters occurred at roughly comparable concentrations of the natural bases and their nucleosides.

4.5 Mechanistic considerations

Aciclovir has little toxicity in either humans or experimental animals, but there is convincing evidence that it can induce genetic changes in a number of mammalian cellular systems, both *in vitro* and *in vivo*. Structural chromosomal aberrations were observed in cultured Chinese hamster fibroblasts and human lymphocytes and in the bone-marrow cells of Chinese hamsters dosed *in vivo*. In addition, an increased frequency of micronucleated cells was observed in mice dosed *in vivo*. These effects are probably consequential to the DNA chain termination activity of aciclovir. It should be noted that the doses required to produce a clastogenic response were much higher than those to which people and experimental animals are exposed. Furthermore, the doses of up to 450 mg/kg bw per day that were given to mice and rats by gavage during the two-year tests for carcinogenicity, in which treatment-related tumours did not develop, are unlikely to have produced peak plasma concentrations sufficient to precipitate a clastogenic response. The lowest clastogenic doses were 250 μg/mL in cultured human lymphocytes and 540 μmol/kg bw in mouse bone marrow after intravenous administration. The latter dose would have resulted in an extremely high plasma concentration. The peak plasma concentration in humans receiving a typical dosing regime is about 2 μmol/L, or 0.5 μg/mL.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Aciclovir is an acyclic nucleoside analogue which was first approved for use as an antiviral agent in 1982. It is used in the treatment of herpes simplex, varicella and herpes zoster viral infections. Oral and topical forms of aciclovir are very widely used for mucocutaneous infections. Intravenous preparations are widely used for some infections including encephalitis associated with herpes simplex viral infection and neonatal herpesvirus infection.

5.2 Human carcinogenicity data

The results of one prospective study and an extended observational follow-up indicated no increased risk for cancer among patients with recurrent herpes simplex

infection given aciclovir orally, but, as the studies were not designed to investigate cancer, no conclusion can be drawn.

5.3 Animal carcinogenicity data

Aciclovir was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration. The tumour incidence was not increased in either species.

5.4 Other relevant data

The pharmacokinetics of intravenously administered aciclovir in humans is stable over a wide dose range. The bioavailability of orally administered aciclovir is 15–30%. It is widely distributed, can cross the placenta and is, relative to many other antiviral drugs, slowly removed from plasma. More than half the administered drug is excreted unchanged, while the metabolite 9-carboxymethoxymethylguanine constitutes 8–14% of the dose. Urinary excretion can be markedly reduced in patients with impaired renal function. The pharmacokinetics of aciclovir in dogs is similar to that in humans, but the drug is removed more rapidly from the plasma of rats. Virtually all of the drug is recovered unchanged from dosed rats.

Adverse effects of aciclovir have been reported extremely rarely in people who have received oral or topical formulations. Higher doses are given intravenously in cases of serious illness, and most of the side-effects have been reported after such usage. The most common serious adverse effects are neurotoxicity and nephrotoxicity. Dogs and rats also show nephrotoxicity when treated at high doses.

Insufficient human data were available on the reproductive and prenatal effects of aciclovir. No developmental toxicity was reported in mice, rats or rabbits given doses over several days during gestation.

The available mutagenicity data indicate that aciclovir is primarily clastogenic at high concentrations, consistent with its action as a DNA chain terminator.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of aciclovir.

There is *inadequate evidence* in experimental animals for the carcinogenicity of aciclovir.

Overall evaluation

Aciclovir is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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