PREDNIMUSTINE

1. Chemical and Physical Data

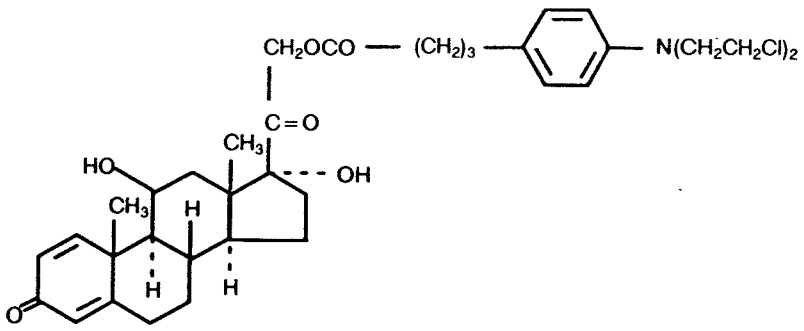
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 29069-24-7

Chem. Abstr. Name: Pregna-1,4-diene-3,20-dione, 21-(4-{4-[bis(2-chloroethyl)amino]phenyl}-1-oxybutoxy)-11,17-dihydroxy-(11β)-

Synonyms: Prednisolone, 21-(4-{*para*[bis(2-chloroethyl)-αβ-amino]phenyl}-butyrate); 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione-21-(1-{*para*-[bis-(2-chloroethyl)amino]phenyl}butyrate); Leo 1031; NSC 134087

1.2 Structural and molecular formulae and molecular weight



$C_{35}H_{45}Cl_2NO_6$ Mol. wt: 646.66

1.3 Chemical and physical properties of the pure substance

From Windholz (1983), unless otherwise specified

(*a*) *Description*: Crystals from methanol-water

(*b*) *Melting-point*: 163-164°C

(*c*) *Optical rotation*: $[\alpha]_D^{24} = +92.9°$ (c = 1.06 in chloroform)

(*d*) *Solubility*: Practically insoluble in water; soluble in ethanol, acetone, chloroform and methanol (Reynolds, 1989)

1.4 Technical products and impurities

Trade names: Mostarine; Sterecyt; Stéréocyt

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Prednimustine can be produced by the esterification of chlorambucil with prednisolone (Fex *et al.*, 1970). It is synthesized in Sweden.

Prednimustine is not known to occur naturally.

2.2 Use

Prednimustine is a cytostatic agent. It has been used in the treatment of various malignancies, including chronic lymphatic leukaemia and non-Hodgkin's lymphomas, at daily oral doses of 140-200 mg for three to five days or continuously at 20-30 mg per day (Reynolds, 1989; Szanto *et al.*, 1989). It has also been tested for use in the treatment of breast cancer (Loeber *et al.*, 1983; Rankin *et al.*, 1987).

2.3 Analysis

Prednimustine has been quantified in plasma by high-performance liquid chromatography (Newell *et al.*, 1979). It has also been quantified after hydrolysis to chlorambucil, by gas chromatography-mass spectrometry (Jakhammer *et al.*, 1977) and high-performance liquid chromatography (Workman *et al.*, 1987).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Rat: Four groups of 30 female Sprague-Dawley rats, 100 days of age, received prednimustine [purity unspecified] at 12 mg/kg bw in a vehicle consisting of

carboxymethylcellulose, Tween 80 and glucose in water by gavage once, twice, 4.5 or nine times per month for 18 months. The last group had significantly reduced survival. A group of 120 female rats received the vehicle alone by gavage nine times per month for 18 months. A significant increase ($p < 0.01$; Peto test: Peto *et al.*, 1980) in the incidence of squamous-cell carcinomas of the external auditory canal was observed (controls, 0/30; once per month, 0/30; twice per month, 1/30; 4.5 times per month, 2/30; nine times per month, 2/30). No increase in the incidence of other tumours was observed (Berger *et al.*, 1985, 1986).

(*b*) *Carcinogenicity of metabolites*

Chlorambucil has been evaluated in the *IARC Monographs* (IARC, 1975, 1981, 1987).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Following a subcutaneous injection of radiolabelled prednimustine at 20 mg/kg bw to female Wistar rats, radioactivity appeared gradually in blood plasma over 48 h. The levels of chlorambucil and phenylacetic mustard in plasma were below 5 μM. Radioactivity levels in all tissues studied were lower than those in plasma; in the small intestine, activity peaked at 2-4 h after administration. No or little radioactivity was detected in bone marrow (Newell *et al.*, 1981).

When radiolabelled prednimustine was injected intravenously to baboons, low urinary and biliary excretion was observed. The radioactivity in blood and kidney decreased with time, but it was stable in the liver over the observation period of 6 h. In muscle, prostate, lung, spleen and seminal vesicles, however, radioactivity levels rose after 4 and 6 h (Kirdani *et al.*, 1978).

Prednimustine is hydrolysed completely *in vitro* by rat plasma esterases to chlorambucil and prednisolone (Wilkinson *et al.*, 1978). A cholesterol ester of chlorambucil, originating from prednimustine by acyltransferase-catalysed trans-esterification, was detected when prednimustine was incubated with human, rat or dog plasma *in vitro*. The same ester was identified in plasma of dogs after intravenous injection *in vivo* (Gunnarsson *et al.*, 1984).

(ii) *Toxic effects*

In an acute lethality study, survival of Wistar rats given prednimustine at 128 mg/kg bw subcutaneously was 70% after 21 days. The drug was less toxic than chlorambucil and less toxic than chlorambucil and prednisolone given in combination (Harrap *et al.*, 1977).

In subacute toxicity experiments, the mortality caused by daily oral administrations of prednimustine for four weeks to Sprague-Dawley rats was low

compared to that induced by chlorambucil and prednisolone given together. Mortality in prednimustine-treated animals was about 10% at dose levels of 32 and 64 mg/kg bw. Dose-related lymphopenia was observed, and spleen and adrenal weights were reduced (Fredholm *et al.*, 1978).

No symptom of toxicity was observed during a life-time carcinogenicity study with prednimustine given to Sprague-Dawley rats at 12 mg/kg bw one to nine times per month for 18 months (Berger *et al.*, 1986).

Prednimustine caused a dose-dependent decrease in survival in Chinese hamster V79-4 cells; it was at least three times as toxic as chlorambucil throughout the dose range (Hartley-Asp *et al.*, 1986). Dose-dependent cell death was also observed in the hormone-sensitive S49 mouse lymphoma cell line after incubation for 24 h with prednimustine at 10^{-8} M up to 5×10^{-7} M prednimustine (Harrap *et al.*, 1977).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No data were available to the Working Group.

(*b*) *Humans*

(i) *Pharmacokinetics*

When prednimustine was given orally at doses up to 200 mg, no unchanged drug could be detected in blood (Newell *et al.*, 1979; Ehrsson *et al.*, 1983; Gaver *et al.*, 1983; Newell *et al.*, 1983; Oppitz *et al.*, 1989) or in urine (Kirdani *et al.*, 1978). When prednimustine was given orally at 20 mg, no chlorambucil or phenylacetic mustard was detected in the circulation (Newell *et al.*, 1979, 1983); however, when a higher dose (100 or 200 mg) was given, chlorambucil was detected in blood (Ehrsson *et al.*, 1983; Oppitz *et al.*, 1989). After a dose of 200 mg, phenylacetic mustard was also identified in the circulation (Oppitz *et al.*, 1989), and, after an oral dose of 100 mg, free prednisolone was detected (Sayed *et al.*, 1981). The concentrations of chlorambucil and its metabolites and of prednisolone detected in the circulation after an oral dose of prednimustine were lower than those after equimolar doses of chlorambucil and prednisolone given separately (Sayed *et al.*, 1981; Ehrsson *et al.*, 1983; Oppitz *et al.*, 1989). After a single oral dose of prednimustine, the peak values of chlorambucil and phenylacetic acid mustard in the serum were reached later and the disappearance half-time was longer than after administration of chlorambucil and prednisolone separately (Ehrsson *et al.*, 1983; Oppitz *et al.*, 1989). Three to six hours after a single oral dose of 40 mg/m^2 radiolabelled prednimustine, 50% of the plasma radioactivity could be extracted into organic solvents; the extractable proportion decreased with time and was $<10\%$ after 12-18 h. The terminal

half-time of ten days for prednimustine-derived radioactivity in plasma could be attributed to these covalently bound metabolites (Gaver *et al.*, 1983).

When a trace amount of double-labelled prednimustine (^{14}C in the bischloroethyl group, ^{3}H at positions 6 and 7 of the steroid part) was administered intravenously, ^{14}C and ^{3}H in the urine cochromatographed partially during the first hour after the injection but were fully separated thereafter, indicating that intact prednimustine is excreted in the urine only immediately after injection (Kirdani *et al.*, 1978).

(ii) *Adverse effects*

Leukopenia and thrombocytopenia seem to be dose-dependent and may limit the dose that can be used. Nausea and vomiting are frequent (Könyves *et al.*, 1975; Loeber *et al.*, 1983; Rankin *et al.*, 1987; Szanto *et al.*, 1989).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No adequate studies were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Prednimustine has been used as a cytostatic drug, mainly for the treatment of malignancies of lymphatic tissue.

4.2 Experimental carcinogenicity data

Prednimustine given by oral administration to rats induced a low but significant increase in the incidence of squamous-cell carcinomas of the external auditory canal.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In humans, prednimustine causes leukopenia and thrombocytopenia; in experimental animals, it causes lymphopenia. It is hydrolysed to chlorambucil and prednisolone *in vivo*. (See Appendix 1.)

4.5 Evaluation[1]

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

No data were available from studies in humans on the carcinogenicity of prednimustine.

Overall evaluation

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

5. References

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[1]For description of the italicized terms, see Preamble, pp. 26–29.

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