APPLICATION DATA SHEET

Publication Filing Type: New Provisional
Application Type: Provisional
Title of Invention: ORAL FORMULATIONS OF CYTIDINE ANALOGS

Customer Number Attorney and Correspondence Address: 25871

INVENTORS:

ETTER, Jeffrey B.
1318 Deer Trail Rd.
Boulder, CO 80302
(US Citizen)

ASSIGNEE:
Pharmion Corporation
2525 28th Street
Boulder, Colorado 80301
(Delaware Corporation)

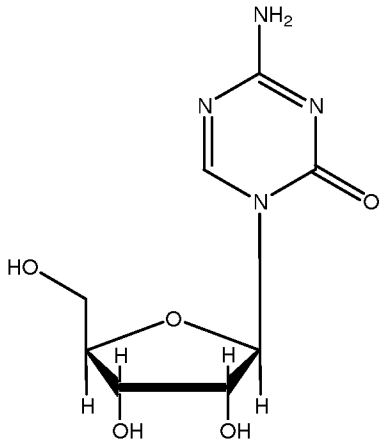
ORAL FORMULATIONS OF CYTIDINE ANALOGS

BACKGROUND OF THE INVENTION

[0001] Cellular proliferative disorders are responsible for numerous diseases resulting in major morbidity and mortality and have been intensively investigated for decades. Cancer now is the second leading cause of death in the United States, and over 500,000 people die annually from this proliferative disorder.

[0002] Nucleoside analogs have been used clinically for the treatment of viral infections and proliferative disorders for decades. Most of the nucleoside analog drugs are classified as antimetabolites. After they enter cells, nucleoside analogs are successively phosphorylated to nucleoside 5'-monophosphates, 5'-diphosphates, and 5'-triphosphates. In most cases, nucleoside triphosphates are the chemical entities that inhibit DNA or RNA synthesis, either through a competitive inhibition of polymerases or through incorporation of modified nucleotides into DNA or RNA sequences. Nucleosides may act also as their diphosphates.

[0003] 5-Azacytidine (also known as azacitidine and 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one; Nation Service Center designation NSC-102816; CAS Registry Number 320-67-2) has undergone NCI-sponsored trials for the treatment of myelodysplastic syndromes (MDS). See Kornblith et al., J. Clin. Oncol. 20(10): 2441-2452 (2002) and Silverman et al., J. Clin. Oncol. 20(10): 2429-2440 (2002). 5-Azacytidine may be defined as having a molecular formula of $C_8H_{12}N_4O_5$, a relative molecular weight of 244.21 and a structure of:

[0004] 

[0005] Azacitidine (also referred to herein as 5-azacytidine herein) is a nucleoside analog, more specifically a cytidine analog. Azacitidine is an antagonist of its related natural

nucleoside, cytidine. Azacitidine, as well as decitabine, i.e., 5-aza-2'-deoxycytidine, are antagonists of decitabine's related natural nucleoside, deoxycytidine. The only structural difference between the analogs and their related natural nucleosides is the presence of nitrogen at position 5 of the cytosine ring in place of oxygen.

[0006] Other members of the class of deoxycytidine and cytidine analogs include arabinosylcytosine (Cytarabine), 2'-deoxy-2',2'-difluorocytidine (Gemcitabine), 5-aza-2'-deoxycytidine (Decitabine), 2(1H) pyrimidine riboside (Zebularine), 2',3'-dideoxy-5-fluoro-3'thiacytidine (Emtriva), N^4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (Capecitabine), 2'-cyclocytidine, arabinofuanosyl-5-azacytidine, dihydro-5-azacytidine, N^4-octadecyl-cytarabine, elaidic acid cytarabine, and cytosine 1-β-D-arabinofuranoside (ara-C).

[0007] In general, oral delivery of members of this class of compounds has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor tissue permeability. For example, these compounds are known to be acid labile and thus unstable in the acidic gastric environment. In the case of azacitidine, ara-C, decitabine and gemcitabine, an enzyme thought to be responsible for a significant portion of drug metabolism is cytidine deaminase. Strategies to improve the oral bioavailability of this drug class have included the use of prodrugs to modify chemical and enzymatic instability, and/or the use of enzymatic inhibitors.

[0008] For example, DeSimone et al describe the ability of azacitidine to induce fetal hemoglobin production in baboons when administered via the intravenous (IV), subcutaneous (SC), or perioral (PO) route. In the case of PO administration the author states that co-administration of THU (tetrahydrouridine) was necessary to achieve fetal hemoglobin induction, however no specific data is provided on the doses or responses observed without THU. Azacitidine doses ranged from 0.25 mg/kg/d to 8 mg/kg/d with co-administration of 20 mg/kg/d THU. Administration of THU alone was shown to result in a significant decrease in peripheral cytidine deaminase activity.

[0009] Neil, et al describe the effect of THU on the pharmacokinetics and pharmacodynamics of inter peritoneal (I.P.) and peri oral (P.O.) azacitidine when administered to leukemic mice. Pharmacokinetic parameters were determined using a bioassay that did not discriminate between azacitidine and its degradation and metabolism products. Inclusion of THU with IP administration had little effect on the clearance or degradation of azacitidine. Inclusion of THU with PO administration significantly increased both C_{max} and $t_{1/2}$. In both

acute and chronic IP dosing the inclusion of THU did not influence the pharmacodymamic effects of azacitidine except at the highest chronic dose which was toxic. Conversely, co-administration of THU with PO azacitidine resulted in increased efficacy at all doses except the highest chronic dose which was again toxic.

[0010] Dunbar, et al describe the administration of azacitidine via IV and PO routes for increased production of total hemoglobin in a β^0-thalassemic patient. Doses of 2 mg/kg/d IV resulted in a measurable increase to hemoglobin levels. Administration of 2 mg/d tid (three times daily) PO with co-administration of THU did not result in increased hemoglobin levels.

[0011] Dover, et al describe administration of azacitidine via the SC and PO routes for increased production of total hemoglobin, fetal hemoglobin and F cells in sickle cell patients. Azacitidine oral bioavailability was assessed by clinical response only. Dover reports that oral doses of azacitidine (2 mg/kg/d) alone or THU (200 mg/d) alone did not result in increased F reticulocyte production. However oral doses of 200 mg/d of THU were observed to result in a significant suppression of peripheral cytidine deaminase activity for several days post administration. When azacitidine was co-administered with THU good clinical response was observed as determined by total hemoglobin, fetal hemoglobin and F cell levels. In fact comparable clinical response was observed with doses of 2 mg/kg/d SC without THU versus 0.2 mg/kg/d PO with co-administration of 200 mg/d THU. Oral doses of azacitidine and THU were prepared by encapsulation at the clinical site. No information was provided with respect to excipients.

[0012] Efforts to increase bioavailability of this class of compounds have also been described in, for example, U.S. Patent Application Publication No. 2004/0162263 (Sands, et al.) In this publication, delivery of azacitidine in an enteric-coated formulation are disclosed such that the drugs are preferably absorbed in the upper regions of the small intestine, such as the jejunum.

[0013] Despite these efforts, a need remains for more effective methods and compositions which increase oral bioavailability of this class of compounds.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 represents a graph showing Absolute Mucosal to Serosal Permeability of Azacitidine in Human Intestinal Tissue with and without Enzymatic Inhibition.

[0015] Figure 2 represents a graph showing Relative Mucosal to Serosal Permeability of Azacitidine in Human Intestinal Tissue with and without Enzymatic Inhibition with Respect to Atenolol.

[0016] Figure 3 represents a graph showing Absolute Mucosal to Serosal Permeability of Azacitidine in Human Colonic Tissue with Various Concentrations of TPGS or Labrafil without Enzymatic Inhibition.

[0017] Figure 4 represents a graph showing Relative Mucosal to Serosal Permeability of Azacitidine in Human Colonic Tissue with Various Concentrations of TPGS or Labrafil without Enzymatic Inhibition.

SUMMARY OF THE INVENTION

[0018] In a first embodiment, the present invention comprises a controlled release pharmaceutical composition for oral administration for enhanced systemic delivery of a cytidine analog comprising a therapeutically effective amount of a cytidine analog and a drug release controlling component which is capable of providing release of the cytidine analog primarily in the large intestine. After ingestion by a patient, the cytidine analog is released primarily in the large intestine.

[0019] In another embodiment, the present invention includes a method for treating a patient having a disease associated with abnormal cell proliferation. The method includes orally administering to the patient a controlled release pharmaceutical composition, comprising a therapeutically effective amount of a cytidine analog and a drug release controlling component which is capable of providing release of the cytidine analog primarily in the large intestine. After ingestion by a patient the cytidine analog is released primarily in the large intestine.

[0020] In another embodiment, the present invention includes a method of increasing the bioavailability of a cytidine analog upon administration to a patient, comprising the following steps. First, provided is a controlled release pharmaceutical composition, comprising a therapeutically effective amount of a cytidine analog and a drug release controlling component capable of providing release of the cytidine analog primarily in the large intestine. Second, the patient ingests the composition, whereupon the composition contacts the biological fluids of the patient's body and increases the bioavailability of the cytidine analog.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.