PRODUCT MONOGRAPH

PrKIDROLASE®
(L-asparaginase)

Powder for Solution 10,000 IU/Vial

Antileukemic Agent

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Control No. 209464

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PART I: HEALTH PROFESSIONAL INFORMATION

PrKIDROLASE®

(L-asparaginase)

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular or intravenous infusion (see Dosage and Administration)	10 000 International Units per vial	Glycine and sodium hydroxide

INDICATIONS AND CLINICAL USE

KIDROLASE® (L-asparaginase) is indicated mainly to induce remissions in acute lymphoblastic leukemia. Remissions have also been obtained in cases of acute myeloblastic and acute myelomonocytic leukemia although these forms are less sensitive to the action of the enzyme. Favorable results have sometimes been obtained with L-asparaginase in certain cases of lymphosarcoma, reticulosarcoma, Hodgkin's disease, chronic lymphocytic leukemia and melanosarcoma.

CONTRAINDICATIONS

Patients with known hypersensitivity to L-asparaginase or to any of the constituents of KIDROLASE®, a hypersensitivity reaction occurring during therapy contraindicates the continuation of treatment.

Patients with hepatic insufficiency, pancreatitis.

Pregnant or lactating women: L-asparaginase has been shown in animals to possess embryotoxic and teratogenic activity; therefore, it should not be used in pregnant patients or lactating women.

Patients who have recently been vaccinated against yellow fever.

Patients who are taking phenytoin (see DRUG INTERACTIONS)

WARNINGS AND PRECAUTIONS

ALLERGIC REACTIONS MAY OCCUR DURING THERAPY WITH KIDROLASE® (L-ASPARAGINASE), ESPECIALLY IN PATIENTS WITH KNOWN HYPERSENSITIVITY TO THE OTHER FORMS OF L-ASPARAGINASE.

IN VIEW OF THE UNPREDICTABILITY OF ADVERSE REACTIONS, KIDROLASE® SHOULD BE USED BY PHYSICIANS EXPERIENCED IN CANCER CHEMOTHERAPEUTIC AGENTS ONLY IN A SETTING WHERE FULL RESUSCITATION FACILITIES ARE IMMEDIATELY AVAILABLE.

KIDROLASE® HAS AN ADVERSE EFFECT ON LIVER FUNCTION IN SOME PATIENTS. THERAPY WITH KIDROLASE® MAY INCREASE PRE-EXISTING LIVER IMPAIRMENT CAUSED BY PRIOR THERAPY OR UNDERLYING DISEASE. IN THE TREATMENT OF EACH PATIENT, THE PHYSICIAN MUST WEIGH CAREFULLY THE POSSIBILITY OF ACHIEVING THERAPEUTIC BENEFIT VERSUS THE RISK OF TOXICITY.

General

KIDROLASE® (L-asparaginase) may be used for maintenance or reinduction treatment; however, if a relapse occurs during maintenance treatment with KIDROLASE®, reinduction should be attempted with another agent.

L-asparaginase may induce allergic reactions. Since the intradermal test is unreliable in detecting the sensitivity of the patients - reactions have been observed after a negative intradermal test and vice-versa - and these reactions regress rapidly with I.V. corticotherapy, it is advisable to administer corticosteroids for a day or 2 before initiating

reinduction treatment. Furthermore, at the time of injection, the appropriate material required to treat anaphylactic shock should be readily available.

When intermittent administration has been used, anaphylactic reactions to L-asparaginase were 3 times more frequent when administered I.V. than when injected I.M. Consequently, the I.M. route is recommended for intermittent administration. (See Dosage and Administration).

At the beginning of treatment, monitoring of blood uricemia should be performed and, if necessary, allopurinol should be administered for as long as required.

Hepatic function tests and blood counts should be monitored regularly during therapy.

Endocrine and Metabolism

Treatment with KIDROLASE® may exacerbate diabetes mellitus. Hyperglycemia has been observed in a number of patients; therefore, glycemia should receive particular attention during treatment, especially in patients with uncontrolled diabetes.

Amylasemia should also be monitored throughout treatment. Treatment should be discontinued in case of an increase in amylasemia levels.

Hematologic

Cerebral thrombosis and hemorrhage have been observed in patients treated with KIDROLASE®. In some of these patients, events may have been attributable to coagulation disorders such as increases in Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), hypofibrinogenemia, decreases in antithrombin III, plasminogen and other coagulation factors (VII, IX, X, VIII).

Blood clotting tests (aPTT, KPTT, Fibrinogen and AT III levels) should be carried out before treatment and before each injection of KIDROLASE® (L-asparaginase).

Replacement therapy should be instituted if fibrinogen is less than 1g/L or ATIII less than 60%. If fibrinogen and AT III cannot be increased, treatment should preferably be suspended and resumed only when the laboratory parameters have returned to normal.

Neurologic

Cerebral thrombosis has been observed in patients treated with KIDROLASE® (see above under Hematologic).

Posterior Reversible Encephalopathy Syndrome (PRES) may occur rarely during treatment with any asparaginase. Symptoms of PRES include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia). Symptoms can be nonspecific, and diagnosis requires confirmation by radiological procedures. It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation of KIDROLASE® may be necessary if PRES is suspected or diagnosed. Expert advice should be sought.

Special Populations

Pregnant Women – See Contraindications

Nursing Women – See Contraindications

Monitoring and Laboratory Tests – see General and Hematologic

ADVERSE REACTIONS

Clinical trials with KIDROLASE® (L-asparaginase) were conducted prior to 1970, and some patient subpopulations participating in those trials might have differed from the patients for whom KIDROLASE® is used today. Furthermore, some of the concomitant chemotherapeutics would have been different than would be administered to those patients today, and the survival rates would have been very different for some of the subpopulations of patients in the clinical trials that

were conducted. All of these factors would have an influence upon the adverse event profile. Therefore, the adverse reaction profile observed in those studies might have differed from what would be observed now in any recent clinical trial, including the frequencies of these adverse events. However, the following information represents the best possible understanding of the Adverse Reactions that have been observed during 35 years of clinical experience with KIDROLASE®.

Hypersensitivity reactions are the most frequent and may include urticaria, laryngeal oedema, bronchospasm, hypotension or even true anaphylactic shock. If these reactions occur, discontinue treatment immediately (see Contraindications).

Side effects of a clinical or biological nature observed in the course of clinical trials with L-asparaginase can be classified as follows:

- Hypersensitivity reactions

  Within one-half to one hour following the injection of L-asparaginase, cases of hypersensitivity reactions have been observed. These consisted of cutaneous manifestations, oedema or, in a small number of patients, an anaphylactic reaction. The latter can be seen after the first injection but it occurs mainly between the 5th and the 9th administration.

- Digestive problems

  Nausea and vomiting generally appear at the beginning of treatment. It may be due directly to the drug itself or be secondary to elevation of BUN and blood uric acid. These side effects are rather frequent but rarely severe enough to necessitate withdrawal of treatment.

  Diarrhea and abdominal pain have been observed infrequently but the precise cause is unknown.

  In rare instances, intestinal perforation has occurred although it has been impossible to establish the exact relationship with L-asparaginase.

- Disturbances of hepatic function

  Abnormalities of hepatic function are quite frequent and may, in some cases, even warrant interruption of treatment. Most characteristics are the following: hypocholesterolemia, hypoalbuminemia, increase of alkaline phosphatase and ALT (SGOT) levels. A weak elevation of the AST (SGPT) and an increase in beta and gammaglobulins shown by protein electrophoresis have also been noted. Cholestatic or hepatocellular liver injury with or without steatosis has also been reported. However, while L-asparaginase hepatotoxicity is in most cases mild and regressive, it can in rare instances induce jaundice which may be severe enough to cause death in those patients who are often in rather poor general condition.

  To prevent these side effects, it is recommended that hepatic function tests be performed at least once a week during L-asparaginase therapy and that the treatment be stopped should any significant changes occur.

  Furthermore, before attempting reinduction with KIDROLASE®, hepatic function should be checked to avoid giving L-asparaginase to a patient already showing abnormal values.

- Inhibition of protein synthesis and Metabolic disturbances
  - clotting disorders including increases in Prothrombin Time (PT) and Thromboplastin Time with hypofibrinogenemia, decreases in antithrombin III, plasminogen and other factors (VII, IX, X and VIII) leading to possible bleeding and thrombotic complications. In consideration of coagulation changes during L-asparaginase treatment, hemostatic function should be checked periodically.
  - hypoalbuminemia;
  - decrease in serum insulin with hyperglycemia;
  - hypertriglyceridemia and hypercholesterolemia;
  - hyperammoniemia, sometimes associated with clinical signs of metabolic encephalopathy such as consciousness disorders with confusion, stupor or coma, resulting from excessive ammonia production induced by the action of KIDROLASE® on endogenous asparagin and glutamine.

- Hematologic risks

  Bone marrow aplasia is exceptional with L-asparaginase and its hematological toxicity is not increased by its association with other antileukemic drugs; nevertheless, the usual blood and bone marrow determinations should be done.

- Other side effects
  - in rare instances, central nervous system disturbances appearing mostly in adults and consisting of mild depression associated with personality disorders, disorientation, delusion, convulsions and pseudo-parkinsonism;
  - in rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens;
  - renal failure;
  - septicemia during a period of bone marrow aplasia;
  - fever due either to the disease itself or to the treatment;
  - less frequently, weight loss, hyperglycemia, acute pancreatitis including fatalities and respiratory distress with retrosternal pressure;
  - cerebral thrombosis;
  - amenorrhea, azoospermia.

DRUG INTERACTIONS

Drug-Drug Interactions

Interactions common to all cytotoxic agents: Due to the increased risk of thrombosis in tumoral diseases, anticoagulant treatment is frequently administered. If oral anticoagulants are given, the high within-patient variability of coagulability in the course of the disease and the potential interaction between oral anticoagulants and anticancer chemotherapy require that INR (or PT) testing be done frequently.

Contra-indicated:

- Yellow fever vaccine because of the risk of lethal systemic vaccine disease.

- Phenytoin, fosphenytoin: Risk of convulsions induced by the decrease in the digestive uptake of phenytoin by cytotoxic agents or risk of increased toxicity or diminished efficacy of cytotoxic agents due to the induction of its liver metabolism.

Associations to be avoided:

- Attenuated live vaccines (other than Yellow fever vaccine) because of the risk of fatal disseminated disease. This is even more likely to occur in subjects already immunocompromised by their disease. Use an inactivated vaccine when available (i.e. poliomyelitis vaccine).

Associations to be used with precaution:

- Phenytoin (when used prior to chemotherapy): in patients already receiving phenytoin, consideration should be given to temporarily associate an anticonvulsant benzodiazepine to avoid the risk of convulsions caused by the decrease in digestive uptake of phenytoin induced by cytotoxic agents.
- Immunosuppressants such as cyclosporin, tacrolimus or sirolimus could cause excessive immunodepression with risk of lymphoproliferation.

Drug-Food Interactions and Drug-Herb Interactions have not been studied

Drug-Laboratory Interactions

None have been observed

DOSAGE AND ADMINISTRATION

Administer KIDROLASE® (L-asparaginase) either intramuscularly, or intravenously into the tubing of a running infusion of an isotonic glucose solution or of normal saline which does not contain a preservative.

Dissolve the enzyme with 4 mL of sterile water for injection (per vial of 10,000 International Units). Rotate gently, do not shake.

- Daily administration

  Daily administration is the most usual method and the least likely to cause side effects. The dosage varies from 200 to 1,000 I.U. per kg per day for 28 consecutive days. After this period, if complete remission is obtained, maintenance therapy is instituted, otherwise induction treatment is continued for another 14 days.

- Intermittent administration

  L-asparaginase may also be administered intermittently with 3 injections per week for 4 weeks using the following dosage schedule:

  - 400 I.U./kg on Monday and Wednesday,
  - 600 I.U./kg on Friday.

  After this period, maintenance therapy is instituted if complete remission is obtained; otherwise, the treatment is continued for another 14 days.

  When intermittent administration has been used, anaphylactic reactions with L-asparaginase were 3 times more frequent when administered I.V. than when injected I.M. Consequently, the I.M. route is recommended for intermittent administration.

- Polychemotherapy

  When L-asparaginase is used in association with other antileukemic drugs, full doses, as stated above, should be administered.

N.B.- The choice of dose and method of administration is made according to the particular circumstances governing each case.

OVERDOSAGE

Two cases of accidental overdosage were reported where children received an injection representing 10 times the normal daily dose. No clinical signs were observed but, in one

case, there was an increase in aspartic and glutamic acid plasma levels.

Patients who receive accidentally an overdose of L-asparaginase should be monitored closely for hyperammoniaemia and, if present, receive appropriate corrective treatment.

ACTION AND CLINICAL PHARMACOLOGY

L-asparaginase exerts an antitumor activity which is directly related to its catalytic action upon the hydrolysis of the extracellular L-asparagine into L-aspartic acid and ammonia. This action is exerted on certain neoblastic cells which are unable to synthesize the L-asparagine needed for their own growth and which must rely upon the extracellular L-asparagine supply to assure their development.

At high dosages, L-asparaginase also shows a marked immunosuppressive effect which has been measured in various in vivo and in vitro tests. Both cell mediated and humoral immunities are affected by this inhibitory effect.

STORAGE AND STABILITY

The product, in powder form, in unopened vials, is stable for up to 24 months at 2 ^{o}C to 8 ^{o}C.

KIDROLASE® (L-asparaginase) contains no preservative. **Reconstitution should be done under strict aseptic conditions.** Reconstituted product when not refrigerated should be used immediately (within 3 hours). If not and storage is required, keep refrigerated (2 ^{o}C to 8 ^{o}C) and use within 72 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Vials of 10,000 International Units.

Non-medicinal ingredients: glycine and sodium hydroxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

L-asparaginase or L-asparagine-amido-hydrolase EC 3.5.1.1. type EC 2, a protein of undetermined constitution, is an enzyme isolated from Escherichia coli.

Its molecular weight is approximately 139,000; it is a white, or almost white, slightly hygroscopic powder which is practically insoluble in methanol, acetone, ether and chloroform but soluble in water. Enzymatic titration shows that L-asparaginase has an activity of approximately 200 units/mg.

DETAILED PHARMACOLOGY

- General Pharmacology

  L-asparaginase does not have any apparent effect on the principal body functions. In the pentobarbital anesthetized dog, L-asparaginase, at a dose of 5,000 U/kg I.V. produces no effect on the ECG, the cardiac rhythm, the blood pressure, the respiratory system or the autonomic nervous system.

  In addition, 5 injections (2-1/2 days apart) of 12,000 U/kg I.V. failed to produce any significant changes in the thromboelastogram and thrombocyte count in the mouse.

- Antitumor activity

  The activity of L-asparaginase has been tested on various tumors, lymphosarcomas and leukemias of animals. One study carried out on 109 leukemias in the mouse revealed that X-ray-induced and spontaneous leukemias are especially responsive to L-asparaginase while those which are viral-induced or caused by chemical agents, are only slightly or not responsive at all.

In addition, experiments with 2 sensitive tumor systems, EARAD-1 leukemia and C_{57}B1/Rho leucosarcomatosis, have demonstrated that the effect of L-asparaginase varies with the number of grafted tumor cells.

Furthermore, in EARAD-1 leukemia, it has been shown that the antitumor activity of the enzyme depends on the dose injected, but that it is not influenced by the parenteral route used.

- Immunosuppressive activity

  In several in vivo and in vitro tests, L-asparaginase exerts a marked inhibitory effect on the manifestations of humoral immunity (antibody production) and of cellular immunity (blast transformation of lymphocytes). In certain other immunological reactions where the participation of both immunological systems is possible, the action of L-asparaginase varies; it does not prolong the survival time of a skin homograft in the mouse but seems to impede the rejection of a non-histocompatible leukemia. It has a marked inhibiting effect in the rat on 2 pathologies which strongly resemble auto-immune diseases: adjuvant-induced arthritis and experimental allergic encephalomyelitis.

- Antiviral activity

  L-asparaginase has been shown to exert an antiviral effect on 3 DNA viruses: vaccina virus, myxoma virus and Herpes simplex. This effect seems to be associated with an action of the enzyme on a cellular reactions requiring L-asparagine and essential to the replication of the DNA molecule.

TOXICOLOGY

- Acute Toxicity

  The acute toxicity of L-asparaginase in the mouse and in the rat when administered by the I.V. route is rather low, the LD_{50} in both species being above 200,000 U/kg; in the cat and the dog, the LD_{50} is in the range of 50,000 U/kg while in the rabbit, the

LD_{50} of the enzyme is about 800 U/kg. The greater toxicity of L-asparaginase in the rabbit is probably due to a greater dependency of this species on L-asparagine rather than to a toxic effect of the enzyme.

- Subacute Toxicity

  In the mouse, the subacute LD_{50} of L-asparaginase administered by the I.V. route for 5 consecutive days is approximately 300,000 U/kg I.V. per day. At a daily dose of 25,000 U/kg I.V., the animals became emaciated, but this more or less normalized after treatment was stopped. Two subacute toxicity studies have been dose in the rat. In the first of these, daily dosages of 200, 800 and 3,000 U/kg I.P. were administered over a period of 14 weeks.

  L-asparaginase did not cause any deaths among the animals; however, a mild periportal steatosis, which was not dose related, was observed in the liver, and a few animals showed changes in the epithelial cells in the testicles or a hypertrophy of the cortex of the thymus with proliferation of the large and medium thymocytes and a decrease in the number of small thymocytes. In the second study, daily doses of 0, 200, 1,000 and 5,000 U/kg I.P. were administered for a period of one month. The only difference observed among the test animals, when compared with the control group, was a curtailment of weight gain at the 2 higher dosages.

  In the rabbit, the subacute LD50=s calculated 7 and 20 days after the end of a 5-day treatment period with L-asparaginase were respectively 1,150 and 760 U/kg I.V. per day.

  A dog injected with 10,000 U/kg I.V. per day for 9 consecutive days responded with anorexia, weight loss, salivation and vomiting. Blood was also observed in the stools and there was a temporary decrease in the red cells.

By contrast, 6 dogs were treated at doses of 0, 200, 800 or 3,000 U/kg I.V., 5 days a week for 13 weeks, and no changes in the hemogram or urinalysis were noted. Vomiting occurred a few hours after the injection in animals receiving the highest dosages. At autopsy, atrophy of the thymus was observed and in one dog treated at the highest dose, a slight fatty infiltration and diffusion of hepatocytes could be seen in the liver.

In the monkey, five injections of 800 or 1,200 U/kg I.V. were given weekly for 4 weeks. At the end of the first week of treatment, the animals treated at the lower dose showed a weight loss accompanied by decreases in the number of reticulocytes and in hematocrit and serum-cholesterol levels. Transitory increases of BSP retention and SGOT levels were also observed. At the end of the treatment, thrombocyte levels were elevated and there was a fatty infiltration of the hepatic cells.

TERATOGENICITY

Investigations of teratogenic activity were conducted in the rabbit and the rat; in both species, L-asparaginase was administered I.V. during the gestation period (on the 8^{th} and 9^{th} day in the rabbit and from the 6^{th} to the 15^{th} day in the rat).

These studies show that:

- in the pregnant rabbit, L-asparaginase exerts significant embryotoxic and teratogenic activities at a daily dose of 50 U/kg I.V.;

in the pregnant rat, a daily dose of 300 U/kg I.V. demonstrates a rather clear embryotoxic activity while a teratogenic effect is observed at a dose of 1,000 U/kg I.V. per day.

REFERENCES

1. SOBIN LH, KIDD JG
   Alterations in protein and nucleic acid. Metabolism of lymphoma 6C3HED-OG cells in mice given guinea pig serum.
   J Exp Med 1966, Jan 1; 123(1):55-74

2. ADAMSON RH, FABRO S
   Antitumor activity and other biologic properties of L-asparaginase (NSC-109229) - A review.
   Cancer Chemother Rep 1968 Oct; (Pt 1) 52(6): 617-626

3. BOIRON M, JACQUILLAT CL, WEIL M *et al.*
   L=asparaginase.
   Presse Med 1968 Nov 16; 76(44):2099-2101

4. MATHE G, AMIEL JL, SCHWARZENBERG L, *et al.*
   Essai de traitement de la leucémie aiguë lymphoblastique par la L-asparaginase.
   Presse Med 1969 Mar 14; 77(18):461-463

5. HASKELL CM, CANELLOS, GP, LEVENTHAL BG, *et al*.
   L-asparaginase toxicity.
   Cancer Res 1969 Apr; 29(4): 974-975

6. BEARD MEJ, CROWTHER D, GALTON DAG, *et al.*
   L-asparaginase in treatment of acute leukemia and lymphosarcoma.
   Br Med J 1970 Jan 34; 1(690):191-195

7. BURGIO GR, ASTALDI A Jr, KRC I, *et al.*
   L-asparaginase and inhibition of the lymphocyte immune reaction.
   Farmaco (Sci) 1970 Feb; 25(2):85-95

8. BURCHENAL JH, KARNOFSKY DA
   Clinical evaluation of L-asparaginase.
   Cancer 1970 Feb; 25(2):241-243

9. CLARKSON B, KRAKOFF I, BURCHENAL J, *et al.*
   Clinical results of treatment with *E.coli* L-asparaginase in adults with leukemia, lymphoma, and solid tumors.
   Cancer 1970 Feb; 25(2):279-305

10. TALLAL L, TAN C, OETTGEN H, *et al.*
    E.coli L-asparaginase in the treatment of leukemia and solid tumors in 131 children.
    Cancer 1970 Feb; 25(2):306-320

11. WHITECAR JP, BODEY GP, HARRIS JE, *et al.*
L-asparaginase (current concepts)
N Engl J Med 1970 Mar 26; 282(13): 732-734

12. MARAL R, GUYONNET JC, JULOU L, *et al.*
Studies on the immunosuppressive activity of L-asparaginase.
Recent Results Cancer Res 1970; 33:160-169

13. HO DHW, CARTER CJK, FREI E III
Clinical pharmacologic studies of L-asparaginase.
Clin Pharmacol Ther 1970 May-Jun; II(3):408-417

14. ADAMSON RH, FABRO S, HAHN MA, *et al.*
Evaluation of the embryotoxic activity of L-asparaginase.
Arch Intern Pharmacodyn 1970; 186:310-320

15. HOLLAND JF, GLIDEWELL O, OHNUMA T
Clinical and laboratory studies with *E.coli* asparaginase.
Colloques Internationaux C.N.R.S. 197, Symposium International sur la L-asparaginase
Paris 28-29-30 Novembre 1970; 267-271

16. BERNARD J, BOIRON M, JACQUILLAT CL, *et al.*
L-asparaginase in acute leukemia - A study of 300 cases.
Colloques Internationaux C.N.R.S. 197, Symposium International sur la L-asparaginase
Paris 28-29-30 Novembre 1970; 281-285

17. PRATT CB, CHOI SI, HOLTON CP
Low-dosage asparaginase treatment of childhood acute lymphocytic leukemia.
Am J Dis Child 1971 May; 121:406-409

18. CAPIZZI RL, BERTINO JR, SKEEL RT, *et al.*
L-asparaginase: clinical, biochemical, pharmacological and immunological studies.
Ann Intern Med 1971; 74: 893-901

19. JAFFE N, TRAGGIS D, DAS L, *et al.*
Comparison of daily and twice-weekly schedule of L-asparaginase in childhood leukemia.
Pediatrics 1971 Apr; 49(4): 590-595

20. ORTEGA JA, FINKLESTEIN JZ, ERTEL I, *et al.*
Effective combination treatment of advanced acute lymphocytic leukemia with cytosine arabinoside (NSC-63878) and L-asparaginase (NSC-109229).
Cancer Chemother Rep 1972 Jun; (Pt 1) 56(3):363-368

21. SHAPIRO AD, CLARKE SL, CHRISTIAN JM, ODOM LF, HATHAWAY WE.
Thrombosis in children receiving L-asparaginase. Determining patients at risk.
Am. J. Pediatr. Hematol. Oncol. 1993 15(4):400-405

22. CETIN M, YETGIN S, KARA A, TUNCER AM, GUNAY M, GUMRUK F, GURGEY, A.
Hyperglycemia, ketoacidosis and other complications of L-asparaginase in chidren with acute Lymphoblastic leukemia.
J. Med. 1994 25(3-4):219-229

23. MITCHELL LG, SUTOR AH, ANDREW M.
Hemostasis in childhood acute lymphoblastic leukemia; coagulopathy induced by disease and treatment.
Semin. Thromb. Hemost. 1995 21(4):390-401

24. PARSONS SK, SKAPEK SX, KUHLMAN C, GELBER RD, NEUFELD EJ, BRUNZELL JD, SALLAN SE, RIFAI N.
Asparaginase-associated lipid abnormalities in children with acute Lymphoblastic leukemia (ALL).
Proc. Annu. Meet. Soc. Clin. Oncol. 1995 14:A1037

25. KEUNG YK, RIZK R, WU XY, COBOS E.
Drug-induced hypertriglyceridemia with and without pancreatitis.
South. Med. J. 1999 92:912-914

26. DOLOY A, ROY S, DJOUSSA KAMBOU S, LEGRAND F, BRION F, RIEUTORD A. The use of sodium benzoate in a ten-fold overdose of asparaginase.
Paediatr. Perinat. Drug Ther. 2002 5(2):59-64