PRODUCT MONOGRAPH

ERWINASE®
(Erwinia L-asparaginase)

Freeze-Dried Powder
for Injection
For IM, SC, or Bolus IV Use
Therapeutic Classification: Cytostatic (LOI XX02)

Jazz Pharmaceuticals France SAS
69006 Lyon
France

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Canadian Distributor:
CGF Pharmatec
3516 Griffith
Montreal, Québec H4T 1A7

PRODUCT MONOGRAPH

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Freeze-Dried Powder for Injection

For IM, SC, or Bolus IV Use

10,000 U/Vial Therapeutic

Classification: Cytostatic

WARNING

IT IS RECOMMENDED THAT ERWINASE (ERWINIA L-ASPARAGINASE) FOR INJECTION BE ADMINISTERED TO PATIENTS ONLY IN A HOSPITAL SETTING UNDER THE SUPERVISION OF A PHYSICIAN WHO IS QUALIFIED BY TRAINING AND EXPERIENCE TO ADMINISTER CANCER CHEMOTHERAPEUTIC AGENTS BECAUSE OF THE POSSIBILITY OF SEVERE REACTIONS, INCLUDING ANAPHYLAXIS AND SUDDEN DEATH. THE PHYSICIAN MUST BE PREPARED TO TREAT ANAPHYLAXIS AT EACH ADMINISTRATION OF THE DRUG.

IN THE TREATMENT OF EACH PATIENT THE PHYSICIAN MUST WEIGH CAREFULLY THE POSSIBILITY OF ACHIEVING THERAPEUTIC BENEFIT VERSUS THE RISK OF TOXICITY. THE FOLLOWING INFORMATION SHOULD BE THOROUGHLY REVIEWED BEFORE ADMINISTERING THE RECONSTITUTED PRODUCT.

CLINICAL PHARMACOLOGY

Action

Erwinia L-asparaginase is effective in inducing remission in patients with acute lymphocytic leukemia (ALL).

Its oncolytic mode of action is based on a metabolic defect in asparagine synthesis of the malignant cells. The leukemic cells have a poorly active asparagine synthetase (1, 2). They depend on an exogenous source of the amino acid asparagine for their protein metabolism and survival (3). Asparaginase hydrolyzes circulating asparagine resulting in the starvation and death of the malignant cells (4). Normal cells that can synthesize asparagine de novo are not affected. Wade et al. (5) first discovered certain Erwinia species to be a commercial source of the oncolytic enzyme. And, MacLennan et al. (6) showed Erwinia L-asparaginase to be serologically (antigenically) distinct from

the E. coli derived *enzyme.* Subsequent clinical findings by Beard et al. (7) and many other clinical investigators (8 - 10) demonstrated there was little or no clinical or immunologic cross-sensitivity between the two asparaginases.

INDICATIONS AND CLINICAL USE

Erwinase (Erwinia L-asparaginase) for Injection is indicated in the therapy of patients with ALL where it is used primarily in combination with other antineoplastic agents to induce remission in children and adults with this disease. It may also be used to treat patients who have developed hypersensitivity (but not anaphylaxis) to L-asparaginase derived from IL coli (8, 9, 11). Erwinase for Injection should not be used as the sole agent for induction unless combination therapy is considered inappropriate.

CONTRAINDICATIONS

Erwinase (Erwinia L-asparaginase) for Injection is contraindicated in patients with pancreatitis or a history of pancreatitis, and in acute hemorrhagic pancreatitis, where in some instances fatalities have been reported following L-asparaginase (Erwinia- or E.coli-derived) administration. The drug is also contraindicated in patients who have had previous anaphylactic reactions to it. Erwinase for Injection should not be given to women who are, or are likely to become, pregnant.

WARNINGS

Because of the unpredictability of adverse reactions to L-asparaginase, it is recommended that this product be used only under the direction of a physician in a hospital setting.

Allergic reactions to Erwinase (Erwinia L-asparaginase) for Injection may occur during the primary course of therapy. If these develop, use of the product should be discontinued. L-asparaginase, whatever its bacterial source, is a protein and therefore there is always the possibility of anaphylaxis. As a result, facilities should be made available for its management during administration.

Once a patient has received L-asparaginase as part of a treatment regimen, retreatment with this agent at a later time is associated with an increased risk of hypersensitivity and anaphylactic reactions. In any patient who has received a previous course of therapy with Erwinase for Injection, retreatment (re-induction) should be considered only if there is no evidence of hypersensitivity to it and if in the judgment of the physician the possible benefits are greater than the increased risks from its use.

L-asparaginase has an adverse effect on liver function in the majority of patients. It is recommended that liver function tests (total protein, albumin, globulin, bilirubin, alkaline phosphatase, SGOT and SGPT) be performed periodically during therapy. Therapy with L-asparaginase may increase pre-existing liver impairment caused by prior therapy or underlying liver disease. Because of this, there is a possibility that L-asparaginase may increase the toxicity of other medications (12).

The administration of IV L-asparaginase concurrently with or immediately before a course of vincristine and prednisone may be associated with increased toxicity (13, 14) (See DOSAGE AND ADMINISTRATION).

PRECAUTIONS

This drug may be a contact irritant and both powder and solution must be handled and administered with care. Inhalation of dust or vapours and contact with skin or mucous membranes, especially those of the eyes, must be avoided. In case of contact, wash with copious amounts of water for at least 15 minutes.

L-asparaginase has been reported to have immunosuppressive activity in animal experiments. Accordingly, the possibility that use of the drug in man may predispose to infection should be considered.

L-asparaginase toxicity is reported to be greater in adults than in children (12).

Laboratory Tests

In vitro studies have shown that L-asparaginase inhibits blastogenesis (15). The fall of circulating lymphoblasts often is quite marked. Normal or below normal leukocyte counts are noted frequently within the first several days after initiating therapy. This may be accompanied by a marked rise in serum uric acid. The possible development of uric acid nephropathy should be borne in mind. Appropriate preventive measures should be taken, e.g., allopurinol, increased fluid intake, alkalization of urine. As a guide to the effects of therapy, the patient's peripheral blood count and bone marrow should be monitored frequently.

Frequent serum amylase determinations should be obtained to detect early evidence of pancreatitis. If pancreatitis occurs, therapy should be stopped and not reinstituted. Blood sugar should be monitored during therapy because hyperglycemia may occur (16).

Drug Interactions

Tissue culture and animal studies indicate that L-asparaginase can diminish or abolish the effect of methotrexate on malignant cells (17, 22). This effect on methotrexate activity persists as long as plasma asparagine levels are suppressed. These results would seem to dictate against the clinical use of methotrexate with the product, or during the period following Erwinase (Erwinia L-asparaginase) for Injection therapy, when plasma asparagine levels are below normal. Laboratory Test Interactions

L-asparaginase has been reported to interfere with the interpretation of thyroid function tests by producing a rapid and marked reduction in serum concentrations of thyroxin-binding globulin within two days after the first dose. Serum concentrations of thyroxin-binding globulin returned to pretreatment values within four weeks of the last dose of L-asparaginase.

Use in Pregnancy

Pregnancy category C. In the New Zealand white rabbit, both E, coli-derived and Erwinia L-asparaginase preparations increased the number of resorption sites and the appearance of viable fetuses with congenital malformations (18).

There are no adequate and well-controlled studies in pregnant women. Therefore, the drug should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers

It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk and as there is a potential for serious adverse reactions in nursing infants from Erwinase (Erwinia L-asparaginase) for Injection, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Allergy/Anaphylaxis

Allergic reactions, including skin rashes, urticaria, arthralgia, respiratory distress, and acute anaphylaxis have been reported (8, 14, 19, 20) (See WARNINGS). Acute reactions to L-asparaginase have occurred in the absence of a positive predictive skin test and during continued maintenance of therapeutic serum levels of the enzyme (14).

In children with advanced leukemia, a lower incidence of anaphylaxis has been reported with IM administration, although there was a higher incidence of milder hypersensitivity reactions than with IV administration (21).

Some authors have commented that the E. coli-derived enzyme produced hypersensitivity reactions more frequently than the Erwinia enzyme (11), although Dellinger (19) failed to demonstrate an appreciable difference in anaphylactic reactions to the two drugs. Data from the Medical Research Council UKALL Trial VIII showed only two minor anaphylactoid reactions: one with E. coli-derived and one with Erwinia L-asparaginase-derived enzyme in a total of 758 patients for whom adverse reaction information was available.

The risk of anaphylactic reactions to Erwinase (Erwinia L-asparaginase) for Injection may be significantly greater in patients who have reacted allergenically to E. coli-produced asparaginase (or pegaspargase). The risk of reaction is related to the total number of doses given (14). It is suspected that this increased risk is probably due to an increased sensitivity of patients to ail foreign antigens since there is little or no cross-reactivity between the enzymes (14).

Fatal hyperthermia, as well as fulminant and fatal pancreatitis, have been reported to occur with E. coli-derived L-asparaginase treatment, but the former reaction has not been associated with the Erwinia derivative. However, a case of severe, acute pancreatitis accompanied by vomiting, fatigue, and epigastric pain has been reported with it.

Hyperglycemia has also been reported with the L-asparaginases (16, 22) although it does appear to be potentiated by prednisone. This can be accompanied by glycosuria and polyuria. Serum and urine acetone usually have been absent or negligible in these patients; this syndrome thus resembles hyperosmolar, nonketotic, hyperglycemia induced by a variety of other agents. This complication usually responds to discontinuance of asparaginase, judicious use of IV fluid, and insulin, but may be fatal on occasion.

In addition to hypofibrinogenemia, depression of various other clotting factors has been reported (23, 24). Most marked has been a decrease in plasma levels of Factors V and VIII with a variable decrease in Factors VII and IX. A decrease in circulating platelets has been reported in low incidence which, together with the increased levels of fibrin degradation products in the serum, may indicate development of a consumption coagulopathy. Bleeding has been a problem in only a minority of patients with demonstrable coagulopathy. However, intracranial hemorrhage and fatal bleeding associated with low fibrinogen levels have been reported (12, 21, 25). Increased fibrinolytic activity, apparently compensatory in nature, also has occurred.

Some patients have shown central nervous System (CNS) effects consisting of depression, somnolence, fatigue, coma, confusion, agitation, and hallucinations varying from mild to severe. Rarely, a Parkinson-like syndrome has occurred with tremor and a progressive increase in muscular tone (12, 25 - 27). These side effects usually have reversed spontaneously after treatment was stopped. Erwinase therapy is associated with an increase in blood ammonia during the conversion of asparagine to aspartic acid by the enzyme. No clear correlation exists between the degree of elevation of blood ammonia levels and the appearance of CNS changes. Chills, fever, nausea, vomiting, anorexia, abdominal cramps, weight loss, headache, and irritability may occur and usually are mild.

Azotemia, usually pre-renal, occurs frequently. Acute renal shut-down and fatal renal insufficiency have been reported during treatment (25). Proteinuria bas occurred infrequently.

A variety of liver function abnormalities bas been reported, including elevations of SGOT, SGPT, alkaline phosphatase, bilirubin (direct and indirect) and depression of serum albumin, cholesterol (total and esters) and plasma fibrinogen (28). Increases and decreases of total lipids have occurred. Marked hypoalbuminemia associated with peripheral oedema has been reported (26). However, these abnormalities usually are reversible on discontinuance of therapy and some reversal may occur during the course of therapy. Fatty changes in the liver have been documented by biopsy. Malabsorption syndrome has been reported (27).

During the period of its inhibition of protein synthesis and cell replication, Erwinase for Injection may interfere with the action of drugs, such as methotrexate, which require cell replication for their cytotoxic effect. L-asparaginase may interfere with the enzymatic detoxification of other drugs, particularly in the liver.

Rarely, transient bone marrow depression has been observed, as evidenced by a delay in return by haemoglobin or hematocrit levels to normal in patients undergoing hematologic remission of leukemia. Marked leukopenia has been reported.

In a retrospective analysis of a recent study conducted by the Medical Research Council which used the UKALL VIII protocol, Erwinia L-asparaginase and E. çoli-derived L-asparaginase were used in a chemotherapeutic remission induction regimen for the treatment of ALL in infants and children as young as 6 months of age. The incidence of adverse reactions occurring in the induction regimen using the two asparaginase preparations is contrasted in the following table (29).

Adverse Events Possibly Related to
L-Asparaginase Administration

UKALL-VIII

Event	Percent (%) Incidence (No. of Cases)	
	E. coli	Erwinia
	N = 275	N = 483
Neurological (coma ± seizures)	4.4% (12)	2.1% (10)
Bleeding	5.5% (15)	3.3% (16)
Pancreatitis	1.8% (5)	0
Diabetes mellitus	1.5% (4)	0.2% (1)
Hepatomegaly	1.1% (3)	0.6% (3)
Malabsorption (> 20% wt. loss)	1.5% (4)	1.4% (7)
Anaphylaxis	0.4% (1)	0.2% (1)
Overall incidence of severe toxicity	16.0% (44)	7.9% (38)
Deaths from above	3.6% (10)	1.9% (9)
Septicemia (proven or clinically strongly suspected)	29.4% (56)	18.0% (87)
Hypofibrinogenemia	2.2% (6)	0.8% (4)
Prolonged PTTK	0.4% (1)	0
Elevated serum hepatic enzyme or bilirubin values	1.8% (5)	0.8% (4)
Glycosuria/hyperglycemia	0.4% (1)	0.4% (2)
Elevated serum amylase	1.1% (3)	0.8% (4)
Wheezing	1.1% (3)	0
Rash	0.7% (2)	0
Pyrexia	0.4% (1)	0.2% (1)
Lactose intolerance	0.7% (2)	0
Recurrent vomiting	0.7% (2)	0.4% (2)
Abdominal distension	0	0.4% (2)
Abdominal pain	0	0.6% (3)

One important point about L-asparaginase adverse reactions is that they are usually reversible and are dose dependent (30).

S YMPTOMS AND TREATMENT OF OVERDOS AGE

No human overdosage information is available. If the enzyme is deemed responsible, cease its use. Treatment is symptomatic.

The approximate, acute IV lethal dose in rats is 500,000 -1,000,000 U/kg. In rabbits, the approximate, acute IV LD_{50} is 2,000 - 5,000 U/kg.

DOSAGE AND ADMINISTRATION

Recommended (Representative) Pharmacotherapeutic Induction Regimen s

When using chemotherapeutic agents in combination with Erwinia L-asparaginase for the induction of remission in adults and children with ALL, regimens are being constantly refined, but are always used in an attempt to provide maximum opportunity for success coupled with avoidance of excessive cumulative toxicity or adverse drug interactions (31). The lowest age range of children studied over-all in trials was two to six months.

Use of IL coli L-asparaginase as the sole induction agent does not achieve the same success in ALL as when used in combination with other cytotoxic drugs (10, 32, 33). Likewise, Erwinase (Erwinia L-asparaginase) should be used alone only when a combination regimen is inappropriate because of toxicity, because of other specific patient-related factors, or in cases refractory to other therapy.

It is recommended that Erwinase for Injection be administered either IM or SC since it has been reported that there is a lower incidence of anaphylaxis and fewer complications than by other routes of administration (21, 34).

When giving Erwinase for Injection by IM or SC routes, the injectable volume of drug should be limited at a single site to 2 mL. If a volume greater than 2 mL is to be administered, two injection sites should be used.

IV Use: Direct Injection - When it is more appropriate to directly administer Erwinase for Injection IV than IM or SC, reconstitute the product as described above by adding 1 mL of Sodium Chloride Injection, USP to the 10,000 unit vial.

Withdraw the volume containing the calculated dose from the vial into a polypropylene syringe within 15 minutes of reconstitution. Do not freeze or refrigerate reconstituted solution and administer within 4 hours or discard.

Based upon the UKALL-VIII (1980-84) clinical study sponsored by the UK Medical Research Council with children under the age of 14 years (i.e. infants under 6 months to age 13) (35), the following regimen is a recommended induction schedule (Day 1 is the first day of therapy). Physicians using a given regimen must be thoroughly familiar with its attendant benefits and risks especially because unfavourable interactions with other drugs have been observed. Discontinue L-asparaginase administration in the presence of severe pancreatitis, abnormal pancreatic laboratory tests, severe liver dysfunction, or possible anaphylaxis. Preferably check on urinary glucose before each dose of the enzyme and check on serum

amylase and insulin levels before it is discontinued.

Induction Regimen I (Children. at Average Risk of Relapse Under Six Months Up to 14 Years of Age. Drugs Given Concurrently)

Erwinia L-Asparaginase: Beginning the first dose on Day 4 of Week 1, 6000 U/m body surface IM 3 times weekly for 9 doses (3 weeks' dosage), even if the patient is thrombocytopenic.

Allopurinol: 10 mg/kg orally begun 24 hours before cytotoxic agents are begun and for 14 days unless remission supervenes.

Vincristine Sulfate: 1.5 mg/m (maximum single dose, 2 mg) IV once weekly for 5 weeks, starting on Day 1 of Week 1.

Prednisone: 40 mg/m^2 daily orally in 3 divided doses from beginning of Week 1 to end of Week 4.

Methotrexate: Two, 6-12 mg intrathecal doses, depending on cerebrospinal fluid (CSF) volume/age of patient, on Days 1 and 15, with a 2-week interval between each dose, for the first 4 weeks.

Daunorubicin Hydrochloride: Some patients may also receive this cytotoxic antibiotic: 45 mg/m /day for 2 days by IV infusion (Days 1 and 2 of induction).

Induction Regimen II

Based upon the UKALL-IX *study* (1980-85) a more intensive drug regimen than I, children over 14
years and adults may be benefited with this regimen:
Erwinia L-Asparaginase: 10,000 U/m^2 SC on Days 1, 3, 5 of Week 4 and Day 1 of Week 5.

Allopurinol: Pretreatment with 300 mg orally daily up to 14 days prior to cytotoxic drug commencement.

Prednisolone: 40 mg/m^2 orally daily for 4 weeks, reducing to zero dose over following week.

Vincristine Sulfate: 1.5 mg/m^2 (maximum dose, 2 mg) IV weekly for 3 weeks.

Mercaptopurine: 70 mg/m^2 orally daily during Weeks 4-5.

Methotrexate IV Infusion: 500 mg/m (3 infusions with '/$_3$ of dose of methotrexate given as rapid IV injection and remaining /$_3$ dose given as infusion in sterile saline over 6 hours) at Weeks 6-10 (at intervals of about 10 days) with folinic acid rescue [12 mg/m IV 24 hours after beginning of infusion (i.e., 18 hours after end of the methotrexate infusion)].

An equally effective alternative induction schedule to regimen II, but without methotrexate is:

Induction Regimen III (Children Over 14 Years of Age and Adults)

Erwinia L-Asparaginase: 10,000 U/m^2 SC 3 times weekly starting on Week 4 for 4 weeks.

Allopurinol: 300 mg daily before starting the antileukemic therapy.

Prednisolone: 40 mg/m^2 orally daily for 3 weeks, tailing to zero dose over following week.

Vincristine Sulfate: 1.5 mg/m^2 (maximum 2 mg) IV weekly for 4 weeks and then on Day 1 of Week 6.

Daunorubicin Hydrochloride: 45 mg/m IV on Day 1 of Weeks 1, 4, and 6.

It is important to note that Erwinase for Injection administered concurrently with or immediately before a course of vincristine and prednisone therapy may result in increased toxicity (14).

When asparaginase is used as the sole induction agent for children or adults, the recommended dosage regimen is 200 U/kg/day IV for 28 days (12, 25, 36, 38), but the remissions are of short duration (1-3 months).

Erwinia L-asparaginase for Injection may be used as a direct substitute for E. coli L-asparaginase when hypersensitivity occurs to the latter enzyme (9, 10, 14, 37), but cautiously.

The above cited regimens do not preclude a need for special therapy directed towards the prevention of CNS (sanctuary) leukemia.

Patients undergoing induction therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity. Such adjustments should always involve decreasing dosages of one or more agents or discontinuation depending on the degree of toxicity. Patients, who have received a course of Erwinase for Injection, if retreated, may have an increased risk of hypersensitivity reaction (14). Therefore, retreatment should be undertaken only when the benefit of such therapy is weighed against the increased risk (see WARNINGS).

PHARMACEUTICAL INFORMATION

Drue Substance

- ProperName: Erwinia L-asparaginase
- Common Name: Erwinia L-asparaginase; Erwinia Asparaginase (USAN); Crisantaspase (BAN)
- Chemical Name: L-asparagine amidohydrolase
- Molecular Weight: About 135,000 (four amino acid subunits, each with a molecular weight of about 35,000)
- Physical Form: White crystalline powder
- Solubility: Freely soluble in water and practically insoluble in methanol, acetone, chloroform
- Specific Activity: Equal to or greater than 600 U/mg protein
- Iso-Electric Point (pi): 8.6

Description/Composition

Erwinase® (Erwinia L-asparaginase) for Injection contains the purified enzyme L-asparagine amidohydrolase (L-asparaginase, NSC-106977) derived from the non-human (plant) pathogen Erwinia chrysanthemi (née Er. carotovora). Its activity is expressed in terms of units (U) according to the rules of the International Union of Biochemistry. Each vial contains 10,000 U of Erwinia L-asparaginase, 0.50 mg sodium chloride BP, and 5.0 mg of glucose (dextrose monohydrate) BP. It contains no preservatives.

Stability and Storage Recommendations

The unreconstituted product is quite stable to temperature extremes, but overall the drug should be stored at 2-8 °C (refrigerator temperature) for the duration of the expiry date found on the vial label and multi-vial carton labelling. Do not use beyond the expiry date.

Reconstituted Solutions

Reconstitution of the drug product is performed with 1 - 2 mL of sodium chloride (0.9%) solution for injection (Sodium Chloride Injection, USP) and the reconstituted material is administered within 15 minutes of reconstitution, or if this is not possible, stored at room temperature within a glass or polypropylene syringe for up to 4 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use otherwise. When reconstituted, Erwinia L-asparaginase for Injection should be a clear, colorless solution. If the solution should become cloudy, discard. When reconstituted as indicated, the solution has a pH of 6.0 - 7.5 and is isotonic with blood.

DO NOT USE STERILE WATER FOR INJECTION USP AS SOLVENT as the resultant product is not isotonic and may be painful upon injection. Dissolve by gentle mixing, avoiding formation of bubbles, with minimal contact with the stopper. Do not vigorously shake the reconstituted vial, as a loss of enzymatic potency may result. Contact with the siliconized rubber stopper may possibly denature the reconstituted drug with the formation of a few minute filaments (thread-like wisps) of transiently insoluble material. If they appear, they may be filtered out with a sterile 5 µ filter during administration. The effect is not progressive and does not significantly affect potency.

Parenteral Products

See the Reconstituted Solutions paragraph immediately above.

Special Instructions

See the general precautionary information given above.

AVAILABILITY OF DOSAGE FORMS

Description/Composition

Erwinase (Erwinia L-asparaginase) for Injection is supplied as a white, freeze-dried powder in clear glass, 3 mL capacity vials, 20 vials per carton, for reconstitution before use. Each vial contains 10,000 U Erwinia L-asparaginase, 0.50 mg sodium chloride BP, and 5.0 mg glucose BP. It contains no preservatives. The product reconstituted with Sodium Chloride Injection, USP is for IM (preferably), subcutaneous, or IV (bolus) injection.

PHARMACOLOGY

Animal Pharmacology

The anti-tumor activity of Erwinia L-asparaginase, like that of the E. coli enzyme, is essentially a result of the catalytic deamination of ubiquitous asparagine, essential to RNA and DNA synthesis and cell proliferation, to aspartic acid with the release of ammonia. With the loss of the amino acid and failure of susceptible tumor tissues to generate endogenous asparagine via increased asparagine synthetase activity, asparagine is depleted in the tumor and a selective regression of that tissue results.

Animal Pharmacokinetics

Plasma levels following IV injection of Erwinia L-asparaginase into laboratory rabbits fall rapidly: clearance obeys first order kinetics and shows a $T'/_2$ of 11 hours (39); in mice, IP injection results also in a first order kinetic clearance and shows a $T'/_2$ of 7.5 hours (39).

Human Pharmacokinetics

In man, plasma asparagine levels fall rapidly after IV administration; and the Erwinia enzyme is absent from the blood seven days after a single IM injection of 25,000 U/m^2 .

In several adult ALL patients, already sensitized to E. coli L-asparaginase. the IV administration of Erwinia L-asparaginase cleared from the plasma with a half-life ($T\ V_2$) of 7-13 hours, decreasing with first order kinetics as in the case of the E. coli derivative (8). The $T\ V_2$ is shorter with the Erwinia enzyme and is longer with that of the latter, which is about 14-22 hours following IV dosing (27). Asselin and Cohen (40), using IM maintenance doses, confirmed first order kinetic clearance with both enzymes in ALL children and found serum $T\ V_2$ of the IL coli enzyme to be about 40 hours compared to that of the Erwinia enzyme, which was about 15.4 hours. And, in an extension of this work, these researchers (41) found the mean serum $T\ V_2$ for Erwinia L-asparaginase ranged from 12.5 to 18.7 hours after a single 25,000 U/m^2 IM induction dose in newly diagnosed ALL children and was statistically shorter than the $T^{1/2}$ for the E. coli enzyme (1.24 days) given at the same dose and the pegalated variant (5.7 days), given at 2500 U/m^2 IM.

The partitioning of Erwinia L-asparaginase between lymph and blood shows that this enzyme, in contrast to the K coli derivative, does not penetrate the capillary endothelia well because negligible amounts are found in the lymph (42): hence, the drug seems to confine itself to the blood compartment of man.

Also, while not crossing the blood-brain barrier itself, the drug completely reduces almost equally for 3-5 days, the CSF levels of L-asparagine [60 - 70% of children (3 days) and 25 - 35% (5 days)] when given IM in standard dosage (10,000 U/m^2 every 3 days) for induction or when given in standard or high (25,000 U/m^2 weekly) dosage in the post-remission period (43).

TOXICOLOGY

Animal Toxicity

Mice - Erwinase (Erwinia L-asparaginase) for Injection was administered in a single dose intraperitoneally (IP) to two groups of twenty mice each. Mortality at the higher treatment level of 1,000,000 U/kg was approximately 30%. Only eight percent of the animas died after receiving the lower dosage of 500,000 U/kg. Death occurred within seven days of dosing and was preceded by diuresis. Macroscopic pathologic examination of animas that died revealed subdural hemorrhage. Microscopic examination revealed dilation and cytoplasmic vacuolization of the renal tubules.

Rats - Acute IV administration to individual groups of ten rats produced total mortality at dosages of 500,000 U/kg and above. Mortality at 200,000 U/kg was 40%. Death occurred within 79 hours of dosing and was preceded in most cases by varying degrees of piloerection and tremoring. Macroscopic examination of tissues from animals that died revealed subdural hemorrhage. Microscopy revealed dilation of renal tubules and apparent depletion of lymphoid cells in the spleen. In a second similar study, ail animals in the high dose group (100,000 U/kg) and 50% of the animals in the mid-dose group (50,000 U/kg) died within 21 hours of dosing.

Rabbits - Toxicologically, the rabbit appears to be particularly sensitive to L-asparaginase, possibly due to a long half-life. When injected IV with doses from 2,000 to 20,000 U/kg body weight, mortalities occurred within 21 days of dosing and were preceded by ataxia. Macroscopy of animals that died revealed subdural hemorrhage. Microscopic pathology revealed dilation of the renal tubules.

In a second study, groups of six rabbits were acutely dosed with 5,000, 10,000 and 20,000 U/kg of the enzyme. Deaths in ail groups occurred within 18 days of dosing and were preceded by loss of appetite and ataxia. Congestion of the lungs, pale kidneys, and subdural hemorrhage were noted.

Dogs - Daily IV injections for 28 days at 5,000 U/kg/day caused no deaths. There was loss of weight and initial vomiting, but at autopsy, there were no abnormal findings.

Rhesus When dosed IV at 2,000 U/kg/day for five days the following

Monkey - observations were noted: slight weight loss and anaemia, but it was felt that this latter effect was due to the multiple bleedings required. Blood chemistry was within normal limits and no fatty liver was found. A comparative IV study of toxicity between Erwinia and IL coli L-asparaginase showed that the Erwinia enzyme was significantly less steatogenic than the E. coli enzyme. Additionally, both enzymes appeared to alter glucose tolerance in a mild, but erratic way. For instance, Erwinia L-asparaginase showed this effect at 10,000 U/kg/day x 5 days, whereas E. coli L-asparaginase delayed the removal of a glucose - load quite significantly after

doses of 1,000 U/kg/day x 5 days.

Carcinogenesis. Mutagenesis, Impairment of Fertility

No separate studies were done on Erwinia L-asparaginase but the IP injection of 2500 U/kg/day for four days of E. coli L-asparaginase in newborn Swiss mice resulted in a small increase in pulmonary adenomas; lymphatic leukemia did not increase.

Similarly there is no separate study of Erwinia L-asparaginase using the Ames microbial mutagen test with or without metabolic activation, but E. coli L-asparaginase at concentrations of 152-909 U/plate was not mutagenic.

There are no available studies on the effects of Erwinia L-asparaginase on fertility.

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