Adagen® (pegademase bovine) in the Treatment of ADA-Deficient Severe Combined Immunodeficiency Disease
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**Important Safety Information**

ADAGEN® (pegademase bovine) Injection is indicated for enzyme replacement therapy for adenosine deaminase (ADA) deficiency in patients with severe combined immunodeficiency disease (SCID) who are not suitable candidates for – or who have failed – bone marrow transplantation. ADAGEN® is recommended for use in infants from birth or in children of any age at the time of diagnosis. ADAGEN® is not intended as a replacement for HLA identical bone marrow transplant therapy. ADAGEN® is also not intended to replace continued close medical supervision and the initiation of appropriate diagnostic tests and therapy (e.g., antibiotics, nutrition, oxygen, gammaglobulin) as indicated for intercurrent illnesses.

There is no evidence to support the safety and efficacy of ADAGEN® as preparatory or support therapy for bone marrow transplantation. Since ADAGEN® is administered by intramuscular injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe.

The optimal dosage and schedule of administration should be established for each patient. Plasma ADA activity and red cell dATP should be determined prior to treatment. The treatment of SCID associated with ADA deficiency with ADAGEN® should be monitored by measuring plasma ADA activity and red blood cell dATP levels.

The following adverse reactions were reported during clinical trials: headache in one patient and pain at the injection site in two patients.

Please see full Prescribing Information on pages 32-33.
Introduction

Severe combined immunodeficiency disease (SCID) is a primary immune deficiency caused by several different genetic defects in the immune system. The syndrome is “severe” because it can prove fatal by 2 years of age and “combined” because it involves both cell-mediated (T lymphocytes) and humoral (B lymphocytes) immunity. Severe compromise in the number and function of these lymphocytes leads to life-threatening infections, diarrhea, dermatitis, and failure to thrive, usually manifested before 3 months of age. Early diagnosis and treatment are critical to prevent potentially fatal consequences.

There are at least 12 known genetic causes of SCID, including mutations in the gene for the enzyme adenosine deaminase (ADA). Deficiency of ADA accounts for about 15% of all cases of SCID. This enzyme catalyzes the metabolism of purine nucleosides, the building blocks of DNA and RNA. In ADA deficiency, toxic substrates accumulate and inhibit lymphocyte maturation and survival. These biochemical effects produce immune dysfunction as well as nonimmunologic pathology.

Unraveling the molecular etiology of ADA-deficient SCID in the 1970s and 1980s permitted new opportunities for therapy, beyond the total isolation technology applied to the “Bubble Boy.” Adagen® (pegademase bovine) Injection represents the first successful application of enzyme replacement therapy for an inherited disease. Adagen® is bovine ADA, modified with strands of polyethylene glycol (PEG) to optimize its therapeutic effect. Approved by the US Food and Drug Administration (FDA) in 1990, Adagen® corrects the underlying metabolic cause of immunodeficiency. It has also been shown to improve immune function and clinical status, as measured by reduced frequency of infection and resumed growth. Importantly, treatment with Adagen® does not preclude subsequent bone marrow transplantation (BMT) with an HLA-identical donor, a treatment that offers a possible cure for SCID.

Today, the outlook for children diagnosed with ADA deficiency has improved. In addition, the devastating consequences of SCID can be avoided. This monograph discusses the important role of Adagen® in managing ADA-deficient SCID.
Overview of SCID

SCID refers to a group of syndromes characterized by complete lack of lymphocyte-dependent adaptive immunity. SCID is a primary immunodeficiency (ie, the immune defect is inherited, not acquired). This is in contrast to secondary immunodeficiencies, which are caused by nonimmune systemic disorders and immunosuppressive treatments.

Mutations in at least 12 different genes have been associated with the pathophysiology of SCID. The most common form of SCID is the X-linked form, which accounts for as many as 50% of cases.

The second most common molecular defect in SCID involves the gene for ADA. This disorder, which can affect as many as 1 in 200,000 live births, is discussed in more detail in the next section and in the remainder of this monograph.

Other genetic mutations in SCID involve Janus kinase 3 (JAK3), recombinase-activating genes (RAG1 and RAG2), and the Artemis gene. Genetic defects are also responsible for a variant of SCID, reticular dysgenesis. This disorder is characterized by bone marrow hypoplasia and disrupted hematopoietic cell lineages.

The frequency of the above genetic defects among infants with SCID treated at Duke University Medical Center is summarized in Table 1.

<table>
<thead>
<tr>
<th>Genetic defect</th>
<th>Frequency, % (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma chain (X-linked)</td>
<td>45.4 (49)</td>
</tr>
<tr>
<td>ADA</td>
<td>14.8 (16)</td>
</tr>
<tr>
<td>JAK3</td>
<td>7.4 (8)</td>
</tr>
<tr>
<td>Unknown autosomal recessive</td>
<td>19.4 (21)</td>
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<tr>
<td>SCID of undetermined type</td>
<td>11.1 (12)</td>
</tr>
<tr>
<td>Reticular dysgenesis</td>
<td>0.9 (1)</td>
</tr>
<tr>
<td>Cartilage hair hypoplasia</td>
<td>0.9 (1)</td>
</tr>
</tbody>
</table>

*Data are based on 108 infants with SCID treated at Duke University Medical Center.
**ADA deficiency**

**ADA gene**
The enzyme ADA is encoded by a gene located on chromosome 20q13.11 (Figure 1). The structure of human ADA has not yet been determined, but murine ADA is 83% identical in sequence (Figure 2). Determining the 3-dimensional structure of murine ADA permitted an understanding of how mutations affect the stability and function of this enzyme.

*Figure 1: Molecular location of the ADA gene*  

![Molecular location of the ADA gene](image)

Adapted from Genetics Home Reference.

*The ADA gene is located on the long arm of chromosome 20 between positions 12 and 13.11.

After X-linked mutations, ADA deficiency is the second most frequent type of SCID.
Figure 2: Structure of recombinant murine ADA


Determining the 3-dimensional structure of murine ADA helped elucidate the effects of mutations on the enzyme’s stability and function.

Role of ADA
ADA is a “housekeeping enzyme” involved in detoxifying purines. It catalyzes the deamination of adenosine (Ado) and 2?-deoxyadenosine (dAdo) to inosine and 2?-deoxyinosine, respectively (Figure 3). Although the enzyme is found in all tissues, the highest levels of ADA are found in the thymus and other lymphoid tissues.

Biochemical hallmarks of ADA deficiency
When ADA is deficient, dAdo is phosphorylated to deoxyadenosine triphosphate (dATP). Accumulation of dATP impairs DNA repair and replication. In addition, ADA deficiency deactivates the enzyme S-adenosyl homocysteine hydrolase (SAHase or AdoHcyase) (Figure 4). In fact, markedly increased dATP concentrations and reduced SAHase activity in erythrocytes are biochemical hallmarks used in diagnosing ADA deficiency. Conversely, erythrocyte dATP or dAXP (total dAdo nucleotides) and SAHase levels are indices of treatment effectiveness.
Understanding the metabolism of purine nucleosides and the toxic effects of ADA deficiency provides insights into the rationale for enzyme replacement therapy with Adagen®.1

Figure 3: Reactions catalyzed by ADA³

Adenosine 2?-deoxyadenosine  Inosine 2?-deoxyinosine


ADA catalyzes the deamination of adenosine and 2?-deoxyadenosine, purine nucleosides produced from the degradation and turnover of RNA and DNA.⁵
**ADA-deficient SCID**

ADA deficiency is distinguished from other primary immunodeficiencies because it is a metabolic disorder.²³ It presents in infancy in 85% to 90% of patients and as delayed or late (adult)-onset combined immunodeficiency in 10% to 15% of patients.²¹

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**In the ADA-deficient state, metabolic abnormalities triggered by elevated concentrations of dAdo and Ado disrupt lymphocyte function, inhibit DNA repair, and induce apoptosis.⁵**

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TdT = terminal deoxynucleotidyl transferase.

Diagnosis of ADA-deficient SCID

Infants with SCID appear healthy at birth; routine newborn assessments do not yield clues to the underlying immune disorder. However, lymphopenia, the classic hallmark of the disease, is already present at birth. Absolute lymphocyte counts are usually <500 cells/µL. Table 2 lists other major criteria for diagnosing the disorder. It is important to note that aggressive supportive therapy for the infectious manifestations of the disease, such as antibiotic therapy, isolation, and antisepsis, can mask the severity of the disease and delay diagnosis of the underlying immune defect.

Infections in patients with delayed/late-onset ADA-deficient SCID (eg, recurrent otitis media, sinusitis, upper respiratory infection) may initially be less severe than those seen in ADA-deficient SCID diagnosed in early infancy. However, by the time these cases are diagnosed, patients have often deteriorated clinically and show evidence of pulmonary insufficiency and autoimmune disease.

Because ADA deficiency appears to exert a cumulative deleterious effect on the immune system, proper diagnosis is essential so that immunorestorative therapy can be promptly initiated. Since the diagnosis is rarely suspected before recurrent infections indicate immune dysfunction, presymptomatic neonatal screening for SCID has been suggested. Prenatal diagnosis can be accomplished through mutation analysis or measurement of ADA activity in trophoblasts cultured from chorionic villus sampling or in cultured amniocytes.
Clinical presentation  Recurrent infection involving pathogens and opportunistic organisms (e.g., thrush, pneumonia, diarrhea, failure to thrive)\(^1\)

Physical finding  Growth failure, evidence of infection, absence of lymph nodes and pharyngeal lymph tissue, characteristic rib abnormalities (“rachitic rosary”)\(^1,24\)

Radiographic features\(^*\)  Absence of a thymic shadow, diminished or absent adenoids\(^1\)

Laboratory findings  Lymphopenia (absolute lymphocyte counts <500 cells/µL)\(^1\)

- Low or absent in vitro lymphocyte function\(^1\)
- Pronounced hypogammaglobulinemia (by 1 or 2 months of age)\(^1\)
- Low or undetectable ADA activity (<1% of normal catalytic activity in erythrocyte hemolysates)\(^2,4\)
- Elevated dATP concentration in erythrocytes\(^1\)
- Reduced SAHase activity (<5% of normal)\(^2,4\)

Molecular genetic testing (sequence analysis)  ADA sequence variants\(^2,4\)

\(^*\)These x-ray abnormalities are not specific for ADA deficiency, but are suggestive of nonspecific reactions to metabolic insult. They may also include cupping/flaring of anterior rib ends, pelvic dysplasia, shortening of vertebral transverse processes, platyspondylia, and unusually thick growth arrest lines.\(^1\)

\(^1\)Patients who have been recently transfused may require ADA testing in another cell type.\(^2,4\)

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**Proper diagnosis is essential, because early initiation of specific therapy is required to restore immune function and prevent progression of pulmonary insufficiency.**\(^1\)
Challenges in the primary care setting

SCID and other primary immunodeficiencies may pose challenges in the primary care setting, as patients typically present with a history of recurrent infections. Because the primary care physician is often the first physician encountered by a patient with immunodeficiency, familiarity with the diagnosis and treatment of these rare disorders is important.

Referral to an immunologist can benefit patients in a number of areas (e.g., interpretation of laboratory findings and other diagnostic tests, genetic counseling, and the selection and implementation of specific therapy for SCID).

Consultation with a clinical immunologist is strongly recommended when there is uncertainty regarding interpretation of screening test results and questions on the choice of advanced diagnostic tests.

Treatment approaches for ADA-deficient SCID

Since the first case of ADA-deficient SCID was reported more than 30 years ago, the molecular etiology and metabolic consequences of the disease have been defined, and this previously fatal disease has become treatable. In the past, transplantation of HLA-identical allogenic bone marrow was the only effective therapy for SCID. Now, other forms of treatment based on specific etiologies have been developed, and the outlook for children born with ADA deficiency is more promising.

SCID is considered an emergent medical problem because infants can rapidly succumb to life-threatening infections. Thus, prompt immunologic evaluation and initiation of immunoreconstitutive treatment are critical to prevent mortality. From the time of diagnosis, aggressive supportive care, including antibiotic therapy, prophylaxis for infection, varying degrees of isolation, and antisepsis, is essential.
Evolving treatment choices
Within the past 2 decades, therapy for ADA-deficient SCID has evolved in 3 areas: transplantation of partially HLA-incompatible bone marrow, experimental gene cell therapy, and enzyme replacement with PEG-modified ADA (Adagen®). The choice of therapy is a complicated decision affected by many factors: the patient’s age and clinical status, distance from a transplant center, expectations of the parents, expertise and experience of the treating physicians, and assessment of risks vs benefits. An algorithm describing the treatment options for ADA-deficient SCID is presented in Figure 5. The pros and cons of each approach are discussed below.

Without treatment, SCID is 100% fatal within the first 2 years of life. 2

Transplantation
BMT/stem cell transplantation (SCT) from an HLA-identical donor has been the preferred treatment for all forms of SCID. This procedure can be performed without cytoreductive conditioning of the patient or depletion of donor T cells. Patients with an HLA-identical sibling have the potential for complete immune reconstitution, with cure rates averaging around 70%, depending on the transplant center. In BMT, engrafted donor T cells provide a source of circulating ADA activity that can reduce Ado toxicity in host lymphocytes. However, ADA-deficient T cells may be more sensitive to Ado toxicity than are B cells, and metabolic correction may not be entirely effective. It appears that engrafted donor T cells may not provide sufficient ADA activity to protect against metabolic toxicity. 1

Further, patients with ADA-deficient SCID appear to be at increased risk of graft failure and transplant-associated morbidity. This predisposition may be due to toxic effects of ADA substrates and other systemic effects of ADA deficiency. Potential complications associated with BMT/SCT include graft-vs-host disease and delayed or incomplete restoration of humoral (B-cell) immunity, necessitating long-term treatment with intravenous immunoglobulin. 24
Patients with ADA-deficient SCID appear to be at increased risk of graft failure and transplant-associated morbidity, possibly because of toxic effects of ADA substrates and other systemic effects of ADA deficiency.²⁵

For the majority of patients with ADA-deficient SCID who lack an HLA-identical, related donor, BMT/SCT from an HLA-haploidentical or HLA-matched, unrelated donor is an option.²⁴,²⁸ However, complications tend to occur more frequently when patients and donors are partially HLA-mismatched.²⁹,³⁰ Cytoablative preconditioning of the patient is sometimes performed to help prevent graft loss and improve recovery of humoral immune function, although pretransplant conditioning is associated with greater morbidity and mortality.²⁴,³¹

Figure 5: Options for treating patients with ADA-deficient SCID²⁵

For patients who do not have an HLA-matched sibling donor, enzyme replacement with PEG-ADA may provide effective metabolic correction²⁵ and does not preclude subsequent transplantation or gene therapy.²⁵ PEG-ADA must not be used as preparatory or support therapy for BMT.
Figure 6 depicts the molecular basis behind the various options for treating ADA deficiency.¹

Figure 6: Correction of metabolic abnormalities through different treatments for SCID¹

The goal of treatment for ADA deficiency is to prevent macrophage-derived purine deoxynucleosides (dAdo) from reaching lymphocytes and to deplete enzyme-deficient lymphocytes of any toxic metabolites formed within them. This can be accomplished via free PEG-ADA in plasma, ADA present in transfused erythrocytes, engrafted donor T cells following marrow transplantation, or ADA gene-transfected T cells.¹

For long-term full clinical benefit in ADA-deficient SCID, correcting the metabolic defect could be as important as correcting the immune defect.\textsuperscript{32}

\textbf{Experimental use of gene therapy}
With the cloning of the ADA gene in the 1980s and the coincidental development of retroviral vectors, gene therapy for ADA-deficient SCID became a viable possibility.\textsuperscript{5} In fact, the first clinical trial of gene therapy for a human disease was initiated for ADA-deficient SCID.\textsuperscript{5} As of the date of publication of this monograph, retrovirus-mediated transfer of the ADA gene into mature T cells and hematopoietic stem/progenitor cells of patients with ADA-deficient SCID is the locus of ongoing investigation.\textsuperscript{1,33} Both the retroviral vector design and the transduction protocols have improved since the early trials.\textsuperscript{5}

In the initial studies, immune reconstitution may have been confounded by the concomitant use of PEG-ADA.\textsuperscript{5,34} Recently, successful restoration of lymphoid development and function through stem-cell gene therapy was reported in 2 patients who did not receive PEG-ADA and underwent nonmyeloablative conditioning.\textsuperscript{32}

In spite of these encouraging results, some experimental gene therapy has been associated with a potentially troubling complication: inadvertent insertion of retroviral vectors into oncogenes, causing T-cell malignancies.\textsuperscript{5,35,36}

Thus, although recent results of gene therapy trials in a few ADA-deficient patients have been promising, this therapy has not been approved by the FDA.

\textbf{Enzyme replacement with PEG-ADA}
When BMT/SCT is not suitable or successful, enzyme replacement therapy with PEG-ADA (trade name, Adagen\textsuperscript{®}) offers a safe and effective option to correct the underlying metabolic cause of immunodeficiency and restore immune function.\textsuperscript{5,37}

It has been more than 30 years since enzyme replacement was first suggested as a treatment for ADA deficiency.\textsuperscript{38} The early finding of restored immune response in cultured lymphocytes of a patient with SCID after exogenous ADA was added prompted further investigation. Initially, ADA replacement used transfusion of irradiated erythrocytes. Although immune function was improved, the response was inconsistent, and the treatment was associated with sensitization to red cell antigens, iron overload, and risk of serious viral infections.\textsuperscript{1}
Enzyme replacement therapy advanced considerably with the development of pegylated ADA (i.e., modification of ADA by covalently attaching strands of the inert polymer monomethoxypolyethylene glycol [PEG]). On a volume basis, the ADA activity of PEG-ADA is approximately 1800 times greater than that of erythrocytes. PEG modification of the ADA molecule slows its clearance and reduces immunogenicity, allowing ADA to achieve its full therapeutic effect.

PEG-ADA provides specific and direct replacement of deficient ADA. By maintaining a high level of ADA activity in plasma, PEG-ADA eliminates extracellular Ado and dAdo, correcting the metabolic toxicity that impairs lymphocyte function. In fact, metabolic correction during PEG-ADA therapy may be more effective than that achieved with chronic transfusion therapy.

Adagen® represents the first successful application of enzyme replacement therapy for an inherited disease. Approved by the FDA in 1990, Adagen® has been used to treat nearly 150 patients with ADA-deficient SCID worldwide. Some lacked an HLA-identical sibling; others had late-onset ADA-deficient SCID and were inappropriate candidates for haploidentical transplantation. Patients treated with Adagen® experienced improved immune function. The remainder of this monograph discusses the experience with Adagen® and its role in the treatment of ADA-deficient SCID.

**Adagen® (pegademase bovine) Injection**

**Description**
Adagen® is a modified enzyme used for enzyme replacement therapy for the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase (ADA).

Adagen® is a conjugate of numerous strands of the inert polymer monomethoxypolyethylene glycol (PEG), molecular weight 5000, covalently attached to the ADA enzyme. The ADA used in the manufacture of Adagen® is derived from bovine intestine.

The structural formula of Adagen® is:

\[
[\text{CH}_3-(\text{OCH}_2\text{CH}_2)_x-\text{O}-\text{C}-\text{CH}_2\text{CH}_2-\text{C}-\text{NH}]_y-\text{adenosine deaminase}
\]

\[x \approx 114 \text{ oxyethylene groups per PEG strand.}\]
\[y \approx 11-17 \text{ primary amino groups of lysine onto which succinyl PEG is attached.}\]

“Systemic ADA replacement has the advantage of rapidly correcting the underlying metabolic cause of immunodeficiency and other pathology due to enzyme deficiency.”
**Indication**

Adagen® is indicated for enzyme replacement therapy for ADA deficiency in patients with SCID who are not suitable candidates for—or who have failed—BMT. Adagen® is recommended for use in infants from birth or in children of any age at the time of diagnosis. Adagen® is not intended as a replacement for HLA-identical BMT. Adagen® is also not intended to replace continued close medical supervision and the initiation of appropriate diagnostic tests and therapy (eg, antibiotics, nutrition, oxygen, gammaglobulin) as indicated for intercurrent illnesses.39

Table 3 reviews factors involved in choosing Adagen® for the treatment of ADA-deficient SCID.40

<table>
<thead>
<tr>
<th>Table 3: Factors involved in the selection of Adagen®40</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HLA-identical sibling donor</td>
</tr>
<tr>
<td>High risk of transplant-associated morbidity</td>
</tr>
<tr>
<td>High probability of graft failure/rejection</td>
</tr>
<tr>
<td>• Delayed or late-onset phenotype</td>
</tr>
<tr>
<td>Patients are not suitable candidates for—or have failed—BMT and:</td>
</tr>
<tr>
<td>• Gene therapy is intended but not immediately available</td>
</tr>
<tr>
<td>• Gene therapy has not produced an adequate response</td>
</tr>
<tr>
<td>• Patients are stable but lack an ideal stem cell donor at time of diagnosis</td>
</tr>
<tr>
<td>• Patients have limited access to a specialized treatment center</td>
</tr>
<tr>
<td>Physician wishes to improve patient’s systemic metabolic status after BMT</td>
</tr>
<tr>
<td>Preference of parents or physicians</td>
</tr>
</tbody>
</table>

**Mechanism of action**

Adagen® provides specific and direct replacement of the deficient enzyme ADA.39 Attachment of PEG strands to the bovine ADA molecule slows the clearance of ADA, increases its circulation half-life, reduces degradation by protease enzymes, lowers binding by host antibodies, and reduces immunogenicity.1 These effects are presumed to result from increased mass and stereochemical effects of the flexible, bulky, and hydrophilic PEG strands.1 On a volume basis, Adagen® possesses approximately 1800 times the ADA activity of erythrocytes; 3 mL of Adagen® contains the ADA equivalent of 10^{12} T lymphocytes.5

Adagen® corrects the metabolic abnormality caused by the accumulation of the purine substrates Ado and dAdo and their metabolites.39 These compounds, which accrue in ADA-deficient cells, are directly toxic to lymphocytes.39 Adagen® maintains sufficient levels of circulating “ectopic” ADA so as to normalize metabolite levels in enzyme-deficient cells.5
This normalization is necessary for improvement in immune function and reduced frequency of opportunistic infections. Improvement in lymphocyte counts and immune function are noted within a few weeks to 6 months of Adagen® treatment.\textsuperscript{39}

\textbf{Pharmacokinetics}

The pharmacokinetics of Adagen® were studied in 6 children with ADA-deficient SCID ranging in age from 6 weeks to 12 years.\textsuperscript{39} This clinical study, which also evaluated safety and efficacy, formed the basis for the approval of Adagen® by the FDA.\textsuperscript{37} It demonstrated that peak plasma levels of Adagen® were reached 2 to 3 days following intramuscular administration. The plasma elimination half-life ranged from 3 to >6 days, with intrasubject variability. Following weekly injections of Adagen® at a dose of 15 U/kg, the average trough level of ADA activity in plasma was between 20 and 25 µmol/h/mL.\textsuperscript{39}

\textbf{History of use}

After experimental findings confirmed the lack of toxicity of free PEG and PEG-ADA and superior levels of circulating ADA activity were achieved with PEG-ADA compared to those with erythrocyte transfusion, the first clinical test of PEG-ADA was undertaken in 1986.\textsuperscript{1,11} The patient studied was a severely ill 45-month-old girl who had failed 2 BMTs and had not responded to transfusion therapy.\textsuperscript{1} With weekly intramuscular injections of 15 U/kg of body weight, PEG-ADA reversed the biochemical consequences of ADA deficiency. Clinical improvement was demonstrated by control of infections and resumption of weight gain.\textsuperscript{11} With the brand name Adagen®, PEG-ADA was approved by the FDA in 1990.\textsuperscript{9} Because it is used in a relatively small number of patients, Adagen® was approved as an “orphan drug.”\textsuperscript{9}

Since 1990, nearly 150 patients have been treated with Adagen® worldwide, and approximately 90 are currently receiving treatment with the drug as of the date of publication of this monograph.\textsuperscript{37} In an evaluation of 119 ADA-deficient patients treated with Adagen® for up to 16.5 years, survival rates were 74% for patients with SCID diagnosed in infancy and 75% for all patients, including those with delayed or late-onset disease.\textsuperscript{5}
ADA-deficient SCID is considered the most difficult form of SCID to treat. For patients whose immunodeficiency persists in spite of long-term treatment with Adagen®, decreased diversity of B lymphocytes, accelerated apoptosis of peripheral lymphocytes, and reduced thymic output have been suggested as mechanisms for the incomplete immune recovery. Evaluating the degree of thymic reserve at the time of Adagen® initiation has been proposed as a means of determining those patients who will benefit most from enzyme replacement.

The physician should determine the best course of treatment for each patient and continually monitor immune function and immune status in patients undergoing Adagen® treatment.

**The human side of SCID and treatment with Adagen®**

Enzyme replacement therapy did not exist during the brief life of David, the “Bubble Boy” with X-linked SCID. Although ADA deficiency is a different type of SCID, the social restrictions and medical demands are comparable. For both types of SCID, early diagnosis and treatment are essential for survival.

For those with ADA-deficient SCID, enzyme replacement therapy with Adagen® is associated with improvements in immune function as well as clinical status, as measured by control of infections and resumption of growth. With sustained clinical improvement, children receiving Adagen® may be expected to lead reasonably normal lives.

**Safety of Adagen®**

Since Adagen® is administered by intramuscular injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe. Clinical experience with Adagen® has been limited. The following adverse reactions were reported during clinical trials: headache in 1 patient and pain at the injection site in 2 patients.

Once effective ADA plasma levels have been established, should a patient’s plasma ADA activity level fall below 10 µmol/h/mL (which cannot be attributed to improper dosing, sample handling, or antibody development), then the patient receiving this lot of Adagen® should be requested to have a blood sample for plasma ADA determination prior to their next injection of Adagen®.
There have been no allergic reactions reported to Sigma-Tau Pharmaceuticals for Adagen® as of October 27, 2008.  

Antibodies to Adagen® may develop in patients and may result in more rapid clearance of Adagen®. Among 10 of 17 patients receiving Adagen® for up to 5.5 years, antibodies to bovine ADA became detectable by the enzyme-linked immunosorbent assay (ELISA), typically between 3 and 8 months of treatment.  

“…based on the experience to date, we are optimistic that children receiving PEG-ADA will be able to lead reasonably healthy, active lives until [curative] procedures are developed and can be applied in a safe, reliable, and effective manner.”

Antibody to Adagen® should be suspected if a persistent fall in preinjection levels of plasma ADA to <10 µmol/h/mL occurs. If other causes for a decline in plasma ADA levels can be ruled out, such as improper storage of Adagen® vials (freezing or prolonged storage at temperatures above 8ºC) or improper handling of plasma samples (eg, repeated freezing and thawing during transport to laboratory), then a specific assay for antibody to ADA and Adagen® (ELISA, enzyme inhibition) should be performed.

A small percentage of patients display enhanced enzyme clearance. Thus, close monitoring of plasma ADA activity is recommended. Plasma ADA should be measured before treatment begins in order to establish baseline. Then, plasma ADA activity should be determined every 1 to 2 weeks during the first 8 to 12 weeks of treatment to establish an effective dose of Adagen®. Between 3 and 9 months, plasma ADA should be determined twice a month and then monthly until after 18 to 24 months of treatment with Adagen®.
Patients who have been successfully maintained on therapy for 2 years should continue to have plasma ADA measured every 2 to 4 months. More frequent monitoring would be necessary if therapy were interrupted or if an enhanced rate of clearance of plasma ADA activity develops. Careful monitoring for signs of deteriorating immune function is also recommended with long-term use, because a gradual decline in T-lymphocyte numbers and function has been observed after 5 to 12 years of treatment with Adagen®.

It is also recommended that red cell dATP levels be regularly monitored. Once the level of dATP has fallen adequately, levels should be measured 2 to 4 times a year during the remainder of the first year of therapy. After that, dATP levels should be assessed 2 to 3 times a year, assuming there has been no interruption in therapy. After 2 years of successful maintenance therapy with Adagen®, dATP levels should be measured twice yearly.

**Efficacy of Adagen®**

Clinical studies show that Adagen® quickly (from a few weeks to up to 6 months) and effectively reverses the metabolic consequences of ADA deficiency. Within 4 to 8 weeks of starting Adagen®, erythrocyte dAXP falls and reaches near normal levels. In addition, erythrocyte SAHase activity increases and also approaches normal levels. These metabolic corrections are achieved in virtually all patients treated for longer than 2 months and are comparable to the metabolic state of healthy individuals with partial ADA deficiency (Figure 7).

Table 4 lists biochemical indices of Adagen® treatment effectiveness.

<table>
<thead>
<tr>
<th>Index</th>
<th>Normal</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte dATP, µmol/mL</td>
<td>&lt;.001</td>
<td>0.056-0.899</td>
<td>0.007-0.015</td>
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<tr>
<td>SAHase, nmol/h/mg protein</td>
<td>4.18±1.9</td>
<td>0.090-0.22</td>
<td>2.37-5.16</td>
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<tr>
<td>Trough plasma ADA activity, µmol/h/mL</td>
<td>12.5-25</td>
<td>&lt;10</td>
<td>~15-35</td>
</tr>
</tbody>
</table>

*Data based on 6 patients (age range, 6 wk-12 y) after 2 months of maintenance treatment with Adagen® (dose used to determine trough plasma ADA activity was 15 U/kg/wk; usual maintenance dose is 20 U/kg/wk).

*Normal range for trough plasma ADA activity calculated from posttreatment levels, which are approximately 2 to 4 times the normal total blood ADA activity.
During the first 3 months of treatment with Adagen®, plasma ADA activity rises above normal levels, erythrocyte dAXP decreases, and SAHase increases.\(^1\)

**Immune restoration**

Improvements in lymphocyte counts and immune function occur within a few weeks to several months of starting Adagen® (Figure 8).\(^3,23\) A dramatic increase in circulating B cells preceded the emergence of mature T cells in several patients.\(^1\) The degree of immune reconstitution varies among patients studied.\(^1\) Prior to treatment with Adagen®, immune status was significantly below normal, as indicated by <10% of normal mitogen responses and circulating mononuclear cells bearing T-cell surface antigens. These parameters improved, although not always to normal, within 2 to 6 months of therapy.\(^39\)

Approximately 20% of patients show only minor improvement in proliferative response of blood mononuclear cells to mitogens. The remainder show responses to mitogens ranging from 30% to >90% of normal. Immune dysregulation may also occur during the initiation of treatment with Adagen®, and some degree of lymphopenia may persist.\(^1\)
As erythrocyte dAXP levels decline, B-cell counts increase within the first month of therapy, and T-cell counts improve within 6 to 12 weeks.\textsuperscript{5,23}

Clinical response

Clinical improvement parallels immune reconstitution.\textsuperscript{1} As metabolic correction proceeds, clinical benefit ensues.\textsuperscript{5} Acute illnesses are often controlled within the first 1 to 3 months of treatment.\textsuperscript{1} By 6 months, opportunistic infections generally no longer pose a threat, and the frequency and duration of respiratory infections and diarrhea have significantly decreased.\textsuperscript{1,10,13} Restrictions on social interactions may often be reduced or removed, as determined by the attending physician.\textsuperscript{10} The overall health status, as defined by control of infections and resumption of growth, improves.\textsuperscript{1,10}

Following metabolic correction, general clinical status, as defined by control of infections and resumption of growth, improves with Adagen\textsuperscript{®} treatment.\textsuperscript{5,10,11}

**Dosage and administration**

Before prescribing Adagen®, the physician should be thoroughly familiar with the details of the drug’s prescribing information (please see pages 32-33 for the complete Prescribing Information for Adagen®). Adagen® is recommended for use in infants from birth or in children of any age at the time of diagnosis.39

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Adagen® should not be diluted or mixed with any other drug prior to administration. 39

The dosage of Adagen® should be individualized. The recommended dosing schedule is 10 U/kg by intramuscular injection for the first dose, 15 U/kg for the second dose, and 20 U/kg for the third dose. The usual maintenance dose is 20 U/kg/wk. Further increases of 5 U/kg/wk may be necessary, but a maximum single dose of 30 U/kg should not be exceeded.39 These guidelines are summarized in Table 5.39

<table>
<thead>
<tr>
<th>Table 5: Dosing guidelines for Adagen®39</th>
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<tr>
<td><strong>Weekly dose</strong></td>
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Plasma levels of ADA more than twice the upper limit of 35 µmol/h/mL have occurred on occasion in several patients and have been maintained for several weeks in 1 patient who received twice-weekly injections (20 U/kg per dose of Adagen®).* No adverse effects have been observed at these higher levels; there is no evidence that maintaining preinjection plasma ADA levels above 35 µmol/h/mL produces any additional clinical benefits.39

*The recommended dosing schedule for Adagen® is 10 U/kg for the first dose, 15 U/kg for the second dose, and 20 U/kg for the third dose. The usual maintenance dose is 20 U/kg/wk. Further increases of 5 U/kg/wk may be necessary, but a maximum single dose of 30 U/kg should not be exceeded.39

**Adagen® remains a valuable and life-saving treatment for patients born with ADA-deficient SCID.6**

Dose proportionality has not been established, and patients should be closely monitored when the dosage is increased. Adagen® is not recommended for intravenous administration. The optimal dosage and schedule of administration should be established for each patient based on monitoring of plasma ADA activity levels (trough levels before maintenance injection) and biochemical markers of ADA deficiency (primarily red cell dATP content).39
Since improvement in immune function follows correction of metabolic abnormalities, maintenance dosage in individual patients should be aimed at achieving the following biochemical goals:

- Maintain plasma ADA activity (trough levels before maintenance injection) in the range of 15 to 35 µmol/h/mL (assayed at 37°C)
- Decline in erythrocyte dATP to <0.005 to 0.015 µmol/mL of packed erythrocytes or ≤1% of the total erythrocyte adenine nucleotide (ATP + dATP) content, with a normal ATP level, as measured in a preinjection sample

In addition, continued monitoring of immune function and clinical status is essential in any patient with a primary immunodeficiency disease and should be continued in patients undergoing treatment with Adagen®.39

For further information concerning the essential monitoring of Adagen® therapy, the prescribing physician should contact Sigma-Tau Pharmaceuticals, Inc., 9841 Washingtonian Blvd. Ste. 500, Gaithersburg, MD 208787.

By telephone, Sigma-Tau can be reached at 1-800-447-0169.

For product information about Adagen®, including information on the essential monitoring of this treatment, physicians can contact Sigma-Tau Pharmaceuticals, Inc., at 1-800-447-0169.

**Conclusion**

The science of ADA-deficient SCID is still evolving, as the first patients to be treated with Adagen® are just now surviving into young adulthood.43 Unless diagnosed and treated early, ADA-deficient SCID is usually fatal. Beyond immunodeficiency, the metabolic disorder may be associated with other serious morbidities, such as hepatic dysfunction and permanent neurological or pulmonary injury.5,23

For patients lacking an HLA-identical sibling donor, Adagen® provides effective treatment.5 Adagen® corrects the underlying metabolic cause of immunodeficiency and improves other pathology caused by ADA deficiency.5 Plasma ADA activity is maintained, erythrocyte dAXP levels are reduced, and SAHase activity returns to normal.1 Along with metabolic correction, clinical status improves as infections are controlled and growth resumes.1,10,11 Although enzyme replacement is not curative,5 it has made this previously fatal disease treatable and allows infants to regain immune function and the chance for a reasonably normal childhood.1,10,13
Continuous treatment with Adagen® is necessary to maintain clinical benefit. Ongoing clinical monitoring to detect signs of infection, deterioration of immune function, or development of neutralizing antibodies to PEG-ADA is advised. Importantly, treatment with Adagen® does not preclude subsequent BMT/SCT or stem-cell gene therapy, should this experimental treatment eventually become available.

As genetic research yields new insights into the pathophysiology and treatment of ADA-deficient SCID, the role of Adagen® will undoubtedly continue to evolve. Most patients treated with Adagen® recover enough immune function to prevent opportunistic infections and improve their clinical course. Although several limitations have been observed with long-term use, Adagen® remains a valuable and life-saving option for patients born with this rare disorder.

The Sigma-Tau Coverage Assistance and Patient Access Program Hotline

The hotline provides general assistance to health care professionals and patients on insurance-related questions.

Call 1-800-345-2252
Monday to Friday: 9:00 AM to 7:00 PM EST

Resources for information on SCID

European Society for Immunodeficiencies (ESID)
http://www.esid.org

Immune Deficiency Foundation
http://www.primaryimmune.org

International Patient Organisation for Patients With Primary Immunodeficiencies
http://ipopi.org

Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center
http://www.jmfworld.com

National Organization for Rare Disorders
http://www.rarediseases.org

Severe Combined Immunodeficiency
http://www.scid.net
References


40. Hershfield MS. Presentation to the Working Party “Inborn Errors” meeting, European Group for Blood and Marrow Transplantation; September 11-14, 2008; Sermione, Italy.


Severe Combined Immunodeficiency Disease Associated with ADA Deficiency

Severe combined immunodeficiency disease (SCID) associated with a deficiency of ADA is a rare, inherited, and often fatal disease. In the absence of the ADA enzyme, the purine substrates adenosine and 2'-deoxyadenosine accumulate, causing metabolic abnormalities that are directly toxic to lymphocytes. The immune deficiency can be cured by bone marrow transplantation. When a suitable bone marrow donor is not available or when bone marrow transplantation fails, non-selective replacement of the ADA enzyme has been provided by periodic irradiated red blood cell transfusions. However, transmission of viral infections and iron overload are serious risks associated with irradiated red blood cell transfusions, and relatively few ADA-deficient patients have benefitted from chronic transfusion therapy.

ADAGEN® (pegademase bovine) Injection provides specific and direct replacement of the deficient enzyme, but will not benefit patients with immunodeficiency due to other causes. In patients with ADA deficiency, rigorous adherence to a schedule of ADAGEN® injection administration can eliminate the toxic metabolites of ADA deficiency and result in improved immune function. It is imperative that treatment with ADAGEN® (pegademase bovine) Injection be carefully monitored by measurement of the level of ADA activity in plasma. Monitoring of the level of deoxyadenosine triphosphate (dATP) in erythrocytes is also helpful in determining that the dose of ADAGEN® (pegademase bovine) Injection is adequate.

Actions

ADAGEN® (pegademase bovine) Injection provides specific replacement of the deficient enzyme. In the absence of the enzyme ADA, the purine substrates adenosine, 2'-deoxyadenosine and their metabolites are toxic to lymphocytes. The direct action of ADAGEN® (pegademase bovine) injection is the correction of these metabolic abnormalities. Improvement in immune function and diminished frequency of opportunistic infections compared with the natural history of combined immunodeficiency due to ADA deficiency only occurs after metabolic abnormalities are corrected. There is a lag between the correction of the metabolic abnormalities and improved immune function. This period of time is variable, and has been reported to be from a few weeks to as long as 6 months. In contrast to the natural history of combined immunodeficiency disease due to ADA deficiency, a trend toward diminished frequency of opportunistic infections and fewer complications of infections has occurred in patients receiving ADAGEN® (pegademase bovine) injection.

Pharmacokinetics

The pharmacokinetics and biochemical effects of ADAGEN® (pegademase bovine) injection have been studied in six children ranging in age from 6 weeks to 12 years with SCID associated with ADA deficiency. After the intramuscular injection of ADAGEN® (pegademase bovine) injection, peak plasma levels of ADA activity were reached 2 to 3 days following administration. The plasma elimination half-life of ADA following the administration of ADAGEN® (pegademase bovine) injection was variable, even for the same child. The range was 3 to > 6 days. Following weekly injections of ADAGEN® (pegademase bovine) injection at 15 U/kg, the average trough level of ADA activity in plasma was between 20 and 25 µmol/hr/mL.

Biochemical Effects

Changes in red blood cell deoxyadenosine nucleotide (dATP) and S-adenosylhomocysteine hydratase (SAHase) have been evaluated. In patients with ADA deficiency, inadequate elimination of 2'-deoxyadenosine caused a marked elevation in dATP and a decrease in SAHase level in red blood cells. Prior to treatment with ADAGEN® (pegademase bovine) injection, the levels of dATP in the red blood cells ranged from 0.056 to 0.689 µmol/mL of erythrocytes. After 2 months of maintenance treatment with ADAGEN® (pegademase bovine) Injection, the levels decreased to 0.007 to 0.015 µmol/mL. The normal value of dATP is below 0.001 µmol/mL. In the same period of time, the levels of SAHase increased from the pretreatment range of 0.09 to 0.22 nmol/hr/mg protein to a range of 2.37 to 5.16 nmol/hr/mg protein. The normal value for SAHase is 4.18 ± 1.9 nmol/hr/mg protein.

INDICATIONS AND USAGE

ADAGEN® (pegademase bovine) Injection is indicated for enzyme replacement therapy for adenine deaminase deficiency in patients with severe combined immunodeficiency disease (SCID) who are not suitable candidates for or who have failed – bone marrow transplantation. ADAGEN® (pegademase bovine) Injection is intended for use in infants from birth or in children of any age at the time of diagnosis. ADAGEN® (pegademase bovine) injection is not intended as a replacement for HLA identical bone marrow transplant therapy. ADAGEN® (pegademase bovine) injection is also not intended to replace continued close medical supervision and the initiation of appropriate diagnostic tests and therapy (e.g., antibiotics, nutrition, oxygen, gammaglobulin) as indicated for intercurrent illnesses.

CONTRAINDICATIONS

There is no evidence to support the safety and efficacy of ADAGEN® (pegademase bovine) injection as preparatory or supportive therapy for bone marrow transplantation. Since ADAGEN® (pegademase bovine) injection is administered by intramuscular injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe.

PRECAUTIONS

General

Any laboratory or clinical indication of a decrease in potency of ADAGEN® (pegademase bovine) injection should be reported immediately by telephone to Enzon Pharmaceuticals, Inc. Telephone 866-792-5172. There have been no reports of hypersensitivity reactions in patients who have been treated with ADAGEN® (pegademase bovine) injection. One of 12 patients showed an enhanced rate of clearance of plasma ADA activity after 5 months of therapy at 15 U/kg/week. Enhanced clearance was correlated with the appearance of an antibody that directly inhibited both unmodified ADA and ADAGEN® (pegademase bovine) injection. Subsequently, the patient was treated with twice weekly intramuscular injections at an increased dose of 20 U/kg, or a total weekly dose of 40 U/kg. No adverse effects were observed at the higher dose and effective levels of plasma ADA were restored. After 4 months, the patient returned to a weekly dosage schedule of 20 U/kg and effective plasma levels have been maintained.

Appropriate care to protect immune deficient patients should be maintained until improvement in immune function has been documented. The degree of immune function improvement may vary from patient to patient and, therefore, each patient will require appropriate care consistent with immunologic status.

Laboratory Tests

The treatment of SCID associated with ADA deficiency with ADAGEN® (pegademase bovine) injection should be monitored by measuring plasma ADA activity and red blood cell ADA levels. Plasma ADA activity and red cell dATP should be determined prior to treatment. Once treatment with ADAGEN® (pegademase bovine) injection is initiated, a desirable range of plasma ADA activity (trough level before maintenance injection) should be 15-35 µmol/hr/mL. This minimum trough level will ensure that plasma ADA activity from injection to injection is maintained above the level of total erythrocyte ADA activity in the blood of normal individuals. Plasma ADA activity (pre-injection) should be determined every 1-2 weeks during the first 8-12 weeks of treatment in order to establish an effective dose of ADAGEN® (pegademase bovine) injection. After 2 months of maintenance treatment with ADAGEN® (pegademase bovine) injection, red cell dATP levels should decrease to a range of ≥ 0.005 to 0.015 µmol/mL. The normal value of dATP is below 0.001 µmol/mL. Once the level of dATP has fallen adequately, it should be measured 2-4 times a year during the remainder of the first year and 2-3 times a year thereafter, assuming no interruption in therapy. Between 3 and 9 months, plasma ADA should be determined twice a month, then monthly until after 18-24 months of treatment with ADAGEN® (pegademase bovine) injection.

Patients who have successfully been maintained on therapy for two years should continue to have plasma ADA measured every 2-4 months and red cell dATP measured twice yearly. More frequent monitoring
would be necessary if therapy were interrupted or if an enhanced rate of clearance of plasma ADA activity develops. Once effective ADA plasma levels have been established, should a patient’s plasma ADA activity level fall below 10 µmol/hr/mL, (which cannot be attributed to improper dosing, sample handling or antibody development) then the patient receiving this lot of ADAGEN® (pegademase bovine) Injection should be requested to have a blood sample for plasma ADA determination taken prior to their next injection of ADAGEN® (pegademase bovine) Injection.

Immune function, including the ability to produce antibodies, generally improves after 2-6 months of therapy, and matures over a longer period. Compared with the natural history of combined immunodeficiency disease due to ADA deficiency, a trend toward diminished frequency of opportunistic infections and fewer complications of infections has occurred in patients receiving ADAGEN® (pegademase bovine) Injection. However, the lag between the correction of the metabolic abnormalities and improved immune function with a trend toward diminished frequency of infections and complications of infection is variable, and has ranged from a few weeks to approximately 6 months. Improvement in the general clinical status of the patient may be gradual (as evidenced by improvement in various clinical parameters) but should be apparent by the end of the first year of therapy. Antibody to ADAGEN® (pegademase bovine) Injection may develop in patients and may result in more rapid clearance of ADAGEN® (pegademase bovine) Injection. Antibody to ADAGEN® (pegademase bovine) Injection should be suspected if a persistent fall in pre-injection levels of plasma ADA to < 10 µmol/hr/mL occurs. If other causes for a decline in plasma ADA levels can be ruled out (such as improper storage of ADAGEN® (pegademase bovine) Injection vials (freezing or prolonged storage at temperatures above 8°C), or improper handling of plasma samples (e.g., repeated freezing and thawing during transport to laboratory)), then a specific assay for antibody to ADA and ADAGEN® (pegademase bovine) Injection (ELISA, enzyme inhibition) should be performed.

In patients undergoing treatment with ADAGEN® (pegademase bovine) Injection, a decline in immune function, with increased risk of opportunistic infections and complications of infection, will result from failure to maintain adequate levels of plasma ADA activity (whether due to the development of antibody to ADAGEN® (pegademase bovine) Injection, to improper calculation of ADAGEN® (pegademase bovine) Injection dosage, to interruption of treatment or to improper storage of ADAGEN® (pegademase bovine) Injection with subsequent loss of activity). If a persistent decline in plasma ADA activity occurs, immune function and clinical status should be monitored closely and precautions should be taken to minimize the risk of infection. If antibody to ADA or ADAGEN® (pegademase bovine) Injection is found to be the cause of a persistent fall in plasma ADA activity, then adjustment in the dosage of ADAGEN® (pegademase bovine) Injection and other measures may be taken to induce tolerance and restore adequate ADA activity.

Drug Interactions

There are no known drug interactions with ADAGEN® (pegademase bovine) Injection. However, Vdarabine is a substrate for ADA and 2'-deoxycoformycin is a potent inhibitor of ADA. Thus, the activities of these drugs and ADAGEN® (pegademase bovine) Injection could be substantially altered if they are used in combination with one another.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies in animals have not been performed with ADAGEN® (pegademase bovine) Injection nor have studies been performed on impairment of fertility. ADAGEN® (pegademase bovine) injection did not exhibit a mutagenic effect when tested against Salmonella typhimurium strains in the Ames assay.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ADAGEN® (pegademase bovine) Injection. It is also not known whether ADAGEN® (pegademase bovine) Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ADAGEN® (pegademase bovine) Injection should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether ADAGEN® (pegademase bovine) Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ADAGEN® (pegademase bovine) Injection is administered to a nursing woman.

ADVERSE REACTIONS

Clinical experience with ADAGEN® (pegademase bovine) Injection has been limited. The following adverse reactions were reported during clinical trials: headache in one patient and pain at the injection site in two patients. The following adverse reactions have been identified during post-approval use of ADAGEN® (pegademase bovine) Injection. Because these reactions are reported voluntarily from a very small population, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hematologic events: hemolytic anemia, auto-immune hemolytic anemia, thrombocytopenia Dermatological events: injection site erythema, urticaria

OVERDOSAGE

There is no documented experience with ADAGEN® (pegademase bovine) Injection overdose. An intraperitoneal dose of 50,000 U/kg of ADAGEN® (pegademase bovine) Injection in mice resulted in weight loss up to 9%.

DOSAGE AND ADMINISTRATION

Before prescribing ADAGEN® (pegademase bovine) Injection the physician should be thoroughly familiar with the details of this prescribing information. For further information concerning the essential monitoring of ADAGEN® (pegademase bovine) Injection therapy, the prescribing physician should contact ENZON Pharmaceuticals, Inc., 685 Route 202/206, Bridgewater, NJ 08807. Telephone 800-792-5172.

ADAGEN® (pegademase bovine) Injection is recommended for use in infants from birth or in children of any age at the time of diagnosis. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits.

ADAGEN® (pegademase bovine) Injection should not be diluted nor mixed with any other drug prior to administration.