CONTRAINDICATIONS (EPOGIN is contraindicated in the following patients.)
Patients with a history of hypersensitivity to EPOGIN, any other erythropoietin preparation, or darbepoetin alfa

DESCRIPTION  In each syringe (0.5 mL) or ampoule (0.5 mL)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Ingredient/content</th>
<th>Inactive ingredient</th>
<th>Dosage form</th>
<th>Color, appearance</th>
<th>pH</th>
<th>Osmotic pressure ratio*4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPOGIN Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syringe 6000</td>
<td>Epoetin Beta (Genetical Recombination), JP *2</td>
<td>L-histidine hydrochloride 0.675mg</td>
<td>Injection (kit including a glass syringe</td>
<td>Colorless</td>
<td>6.8-7.2</td>
<td>About 1</td>
</tr>
<tr>
<td></td>
<td>6000 international units (IU)</td>
<td>Polyoxylethylene (160) polyoxypropylene (30) glycol</td>
<td>containing the solution, or an ampoule)</td>
<td>transparent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPOGIN Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampoule 6000</td>
<td></td>
<td>0.250mg Tonicity agent (Sodium chloride), pH adjuster (Dibasic sodium phosphate hydrate, Sodium hydroxide, Dilute hydrochloric acid*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*2: EPOGIN is manufactured by using ovarian cells of Chinese hamsters.
*3: Dilute hydrochloric acid can optionally be used for pH adjustment.
*4: Osmotic pressure ratio to physiological saline.
**INDICATIONS, DOSAGE AND ADMINISTRATION**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dosage and administration</th>
<th>Maintenance dose</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal anemia in patients undergoing continuous ambulatory peritoneal dialysis (CAPD)</td>
<td>The usual initial dosage is 6,000 IU of EPOGIN once per week. After successful treatment of anemic conditions with medication, the maintenance dose should be adjusted within a range up to 6,000 IU/week, depending on anemic symptoms and the patient’s age.</td>
<td>The target hemoglobin concentration for successful alleviation of anemia is approximately 10 g/dL (hematocrit: 30%).</td>
<td>Administration of EPOGIN should be limited to patients with renal anemia undergoing continuous ambulatory peritoneal dialysis (CAPD) who experience difficulties that impede the performance of ordinary tasks due to anemia, and to patients with renal anemia prior to dialysis (serum creatinine concentration ≥2 mg/dL or creatinine clearance ≤30 mL/min). The target hemoglobin concentration is &lt;10 g/dL (hematocrit: &lt;30%).</td>
</tr>
<tr>
<td>Renal anemia in patients prior to dialysis</td>
<td>Autologous blood donation of more than 800 mL, to be stored for at least one week for a scheduled transfusion during surgery.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous blood donation of more than 800 mL to be stored for at least one week for a scheduled transfusion during surgery</td>
<td>The usual initial dosage is 6,000 IU of EPOGIN once per week, to be injected as slowly as possible. After successful treatment of anemic conditions with medication, the maintenance dose should be adjusted within a range up to 6,000 IU/week, depending on anemic symptoms and the patient’s age.</td>
<td>The target hemoglobin concentration for successful alleviation of anemia is approximately 10 g/dL (hematocrit: 30%).</td>
<td></td>
</tr>
</tbody>
</table>

**PRECAUTIONS**

1. Careful Administration (EPOGIN should be administered with care in the following patients.)

1. Patients with myocardial infarction, pulmonary infarction, cerebral infarction, or those with a history of these conditions who may experience thromboembolism [It has been reported that the administration of EPOGIN increases the viscosity of the blood, and may potentially aggravate or induce thromboembolism. Especially when EPOGIN is administered to collect autologous blood, the patient should be carefully monitored, since there is concern about accelerated blood coagulation following surgery.]

2. Patients with hypertension [The administration of EPOGIN may increase blood pressure or induce hypertensive encephalopathy.]

3. Patients with a history of hypersensitivity to any drug

4. Patients with an allergic predisposition

1. Administration of EPOGIN should be limited to patients with renal anemia undergoing continuous ambulatory peritoneal dialysis (CAPD) who experience difficulties that impede the performance of ordinary tasks due to anemia, and to patients with renal anemia prior to dialysis (serum creatinine concentration ≥2 mg/dL or creatinine clearance ≤30 mL/min). The target hemoglobin concentration is <10 g/dL (hematocrit: <30%).

2. Patients should be carefully interviewed to assess the risk of hypersensitivity reactions such as shock. We recommend performing an intradermal test or a prick test with a small amount of EPOGIN before the first administration, or before resumption of administration after suspended administration. Administer the remaining portion only after confirming that patients do not develop abnormal reactions to EPOGIN.

3. During treatment of EPOGIN, hemoglobin concentration and hematocrit level should be carefully monitored at regular intervals to prevent excessive hemopoiesis (as a general rule, hemoglobin concentration ≥12 g/dL or hematocrit level ≥36%). If excessive hemopoiesis is observed, appropriate measures, such as temporary discontinuation of EPOGIN should be taken.
(4) Since the administration of EPOGIN may increase blood pressure, it should be carefully administered while closely monitoring blood pressure. Also, since hypertensive encephalopathy may develop, it should be carefully administered while monitoring shifts in blood pressure, hematocrit level, and hemoglobin concentration. In particular, hematocrit levels and hemoglobin concentrations must be increased gradually. Patients must be carefully monitored, since hematocrit levels and hemoglobin concentrations may also increase after discontinuation of administration. If increased blood pressure is observed, appropriate measures, such as discontinuation of EPOGIN, should be taken.

(5) Pure red cell aplasia accompanied by production of anti-erythropoietin antibodies may occur. Its occurrence should be suspected if anemia is not improved or rather exacerbated during the treatment. When the disease is diagnosed, EPOGIN should be discontinued and appropriate measures, excluding switching to another erythropoietin preparation or darbepoetin alfa, should be taken.

(6) If EPOGIN is administered to patients with renal anemia prior to dialysis, the following should be considered.

1) Given the difficulty of controlling hydration in patients with renal anemia prior to dialysis, parameters such as water, electrolyte balance, renal function, and blood pressure should be carefully monitored, and as often as for patients undergoing dialysis.

2) Since the anemia-improving effect of EPOGIN may diminish as chronic renal failure advances, changes in parameters, such as serum creatinine concentration or creatinine clearance, should be closely monitored, and appropriate measures, such as dose adjustment or discontinuation of EPOGIN, should be taken.

(7) Since the administration of EPOGIN may cause hyperkalemia, appropriate dietary control is required.

(8) The presence of iron is important for expression of the pharmacological effect of EPOGIN, so an iron preparation should be administered to patients with iron deficiency.

<Autologous blood donation of more than 800 mL to be stored for at least one week for a scheduled transfusion during surgery>

(1) Precautions in use

1) EPOGIN should be administered only to patients who are scheduled to undergo surgery requiring autologous blood transfusions. EPOGIN should not be administered for autologous blood donations in patients with diseases accompanied by impaired hemopoiesis, since the efficacy and safety of EPOGIN in these patients have not been established.

2) During treatment of EPOGIN, hemoglobin concentration and hematocrit level should be carefully monitored at regular intervals to prevent excessive hemopoiesis (as a general rule, hemoglobin concentration ≥14 g/dL or hematocrit level ≥42 %). If excessive hemopoiesis is observed, appropriate measures such as temporary discontinuation of EPOGIN or blood collection should be taken.

3) Patients should be carefully interviewed to assess the risk of hypersensitivity reactions such as shock. We recommend performing an intradermal test or a prick test with a small amount of EPOGIN before the first administration, or before resumption of administration after suspended administration. Administer the remaining portion only after confirming that patients do not develop abnormal reactions to EPOGIN.

4) If any abnormality in hepatic function such as increased AST (GOT) and/or ALT (GPT) is observed, appropriate measures, such as discontinuation of EPOGIN, should be taken.

5) The presence of iron is important for expression of the pharmacological effect of EPOGIN, so an iron preparation should be administered to patients with iron deficiency.

(2) General precautions concerning prededou autologous blood transfusion

1) Prededou autologous blood transfusion should be limited to patients in whom autologous transfusion is expected to be needed based on such information as past experiences, records, etc. at each institution.

2) Before collecting the autologous blood, patients should be fully informed of prededou autologous blood transfusion. Patient consent should be obtained regarding such issues as the nature of the procedure, the disposal of unused blood, etc.

3) It is advisable to avoid autologous blood donation in patients with a hemoglobin concentration <11 g/dL (hematocrit < 33%).

4) The blood should be collected at an interval of about one week. The volume of blood collected should not exceed 400 mL at one time, and is determined based on such information as patient's age, body weight, hematological findings, blood pressure, pulse rate, etc.

5) While collecting the blood, the skin should be thoroughly sterilized using Povidone iodine solution, etc. to maintain the sterility of the blood.

6) To allow for the recovery of plasma proteins, the blood should not be collected within three days of surgery.

7) The blood is collected using a blood collection unit that meets the standards established by the Product Standards for Blood Collection Units Made of Vinyl Chloride Resin (MHW Notification No.399, March 30, 1999) and contains a predetermined amount of a blood preservative (e.g., CPD solution) specified by Human Whole Blood in MRBP. The collected blood should be stored with the closed circuit kept aseptic throughout.

8) Each blood container should state that the contents are autologous blood, and should accompany such information as donor name, collection date, ABO blood typing, etc.
9) The collected blood should be stored in a blood banking refrigerator that operates between 4 and 6°C and is equipped with an automatic temperature-recording device. Transfusion should be performed before the expiration date of each amount of blood collected.

10) Autologous blood should be transfused after ensuring that the collected blood is that of the donor. In cases of any abnormality being noted in appearance of autologous blood, it must not be used.

3. Adverse Reactions

Renal anemia in patients undergoing continuous ambulatory peritoneal dialysis (CAPD)

Subcutaneous administration: 22 adverse reactions to EPOGIN were reported in 18 (5.0%) of 361 patients treated. The major adverse reactions were increased blood pressure (hypertension) in 13 cases (3.6%), nausea, AST (GOT) increased and general malaise in 2 cases respectively (0.6%) (at the end of reexamination for subcutaneous injection in June 2008).

Renal anemia in patients prior to dialysis

Intravenous administration: 142 adverse reactions to EPOGIN were reported in 108 (7.1%) of 1,521 patients treated. The major adverse reactions were increased blood pressure (hypertension/aggravated hypertension) in 40 cases (2.6%), abnormal hepatic function including increased AST (GOT) and/or ALT (GPT) in 36 cases (2.4%) and headache in 11 cases (0.7%) (at the approval of the syringe products 750, 1500 and 3000 IU in February 2000, following the completion of reexamination of the lyophilized products 750, 1500, 3000 and 6000 IU for intravenous injection in March 2004).

Subcutaneous administration: 111 adverse reactions to EPOGIN were reported in 87 (4.6%) in 1,914 patients treated. The major adverse reactions were increased blood pressure (hypertension/aggravated hypertension) in 46 cases (2.4%), increased serum potassium (including hyperkalemia) in 6 cases (0.3%), and increased LDH and creatinine in 5 cases (0.3%) respectively (at the end of reexamination for subcutaneous injection in June 2008).

Autologous blood donation of more than 800 mL to be stored for at least one week for a scheduled transfusion during surgery

Intravenous administration: 102 adverse reactions to EPOGIN were reported in 73 (4.4%) in 1,673 patients treated. The major adverse reactions were abnormal hepatic function including increased AST (GOT) and/or ALT (GPT) in 40 cases (2.4%) and hot flushes (feeling hot) in 9 cases (0.5%) (at the completion of reexamination of the lyophilized products 1500, 3000 and 6000 IU for intravenous injection in March 2004).

(2) Other adverse reactions

When the following adverse reactions are observed, appropriate measures such as dosage reduction or discontinuation should be taken.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>0.1% to &lt;2%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>blood pressure increased</td>
<td>palpitations</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>acne</td>
<td>itching, rash</td>
</tr>
<tr>
<td>Hepatic</td>
<td>hepatic function abnormal (increased AST (GOT), ALT (GPT), LDH, Al-P, total bilirubin, etc.)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>nausea</td>
<td>vomiting, anorexia, abdominal pain, diarrhea</td>
</tr>
<tr>
<td>Sensory</td>
<td>myalgia, dizziness</td>
<td>headache/feeling hot, hot flushes, general malaise</td>
</tr>
</tbody>
</table>

(1) Clinically significant adverse reactions

1) Shock and anaphylaxis

Since shock and anaphylaxis (urticaria, dyspnea, lip edema, pharyngeal edema, etc.) may occur, patients should be monitored closely. If any abnormalities are observed, administration of the drug should be discontinued and appropriate measures should be taken.

2) Hypertensive encephalopathy and cerebral hemorrhage

Due to a rapid increase in blood pressure, hypertensive encephalopathy or hypertensive cerebral hemorrhage accompanied by headache, disturbances in consciousness, convulsion, etc., may occur. Thus, EPOGIN should be administered with care while closely monitoring shifts in such parameters as blood pressure and the like.

3) Myocardial infarction, pulmonary infarction, and cerebral infarction

Since myocardial infarction, pulmonary infarction, or cerebral infarction may occur, patients should be monitored closely. If any abnormalities are observed, appropriate measures such as discontinuation of EPOGIN should be taken.

4) Hepatic function disorder and jaundice

Since hepatic function disorder or jaundice associated with AST (GOT) increased, ALT (GPT) increased, and γ-GTP increased may occur, patients should be monitored closely. If any abnormalities are observed, appropriate measures such as discontinuation of EPOGIN should be taken.

5) Pure red cell aplasia

Pure red cell aplasia accompanied by production of anti-erythropoietin antibodies may occur. When the disease is confirmed, EPOGIN should be discontinued and appropriate measures should be taken.
4. Use in the Elderly

*Renal anemia in patients undergoing continuous ambulatory peritoneal dialysis (CAPD)* and *Renal anemia in patients prior to dialysis*

When administering EPOGIN to elderly patients, parameters such as blood pressure, hemoglobin concentration and hematocrit should be frequently measured so that the dosage and administration frequency can be adjusted accordingly. [The elderly often have reduced physiological function and are apt to have cardiovascular complications such as hypertension.]

*Autologous blood donation of more than 800 mL to be stored for at least one week for a scheduled transfusion during surgery*

1. When administering EPOGIN to the elderly, cardiovascular function should be monitored closely and frequently to detect any cardiovascular or cerebrovascular abnormalities. [The elderly often have reduced physiological function.]
2. When administering EPOGIN, measure hemoglobin concentration frequently and adjust the administration frequency, period, and dosage accordingly. [The elderly often have reduced hematopoietic function.]

5. Use during Pregnancy, Delivery or Lactation

Administration of EPOGIN is not recommended to pregnant women, and women who may be pregnant. When the treatment is necessary in such women, EPOGIN should be used only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of EPOGIN in pregnant women has not been established.]

6. Pediatric Use

The safety of EPOGIN in children born underweight, neonates, and infants has not been established (insufficient clinical data).

7. Precautions concerning Use

*Syringe*

Precautions regarding administration

1. Do not mix with other drugs.
2. Following removal of the rubber cap at the tip of the syringe EPOGIN must be used immediately. Discard after use.

*Ampoule*

Precautions regarding preparation

1. Do not mix with other drugs.
2. EPOGIN is supplied in a “one-point-cut ampoule”. The cut point of the ampoule should be wiped with an alcohol swab before opening.

8. Other Precautions

1. It has been reported that among hemodialysis patients with concurrent cardiac failure or ischaemic heart disease, the mortality rate tended to be higher in a group whose target hemoglobin concentration was maintained at 14 g/dL (hematocrit: 42%) than in a group maintained at approximately 10 g/dL (hematocrit: 30%) [1].
2. It has been reported that among patients with pre-dialysis chronic kidney disease administered erythropoiesis stimulating agents to treat nephrogenic anemia, incidence of death and cardiovascular disorders was significantly higher in patients whose target hemoglobin concentration was set at 13.5 g/dL than in patients set at 11.3 g/dL [2].
3. It has been reported that among patients with pre-dialysis chronic kidney disease and concurrent type II diabetes mellitus and nephrogenic anemia, the incidence of stroke was significantly higher in patients administered erythropoiesis stimulating agents with target hemoglobin concentration set at 13.0 g/dL than in patients administered a placebo (If hemoglobin concentration dropped below 9.0 g/dL, erythropoiesis stimulating agents was administered) [3].
4. It has been reported that administration of an erythropoiesis stimulating agents in patients with anemia caused by cancer chemotherapy or radiotherapy shortened their survival time [4, 5].
5. It has been reported that administration of erythropoiesis stimulating agents to patients with anemia due to radiotherapy increased their risk of tumor progression or local recurrence [5, 6].
6. It has been reported that a clinical study (or studies) has shown that there is a higher incidence of thromboembolism in patients with anemia caused by cancer chemotherapy when they are treated with an erythropoiesis stimulating agents than when they are treated with placebo [5, 7].
7. It has been reported that a clinical study (or studies) has shown that there is a higher incidence of death in patients with cancer-related anemia who have not received cancer chemotherapy or radiotherapy when they are treated with an erythropoiesis stimulating agents than when they are administered placebo [5, 8].

Note 5): Administration of erythropoietic stimulating factors to these patients has not been approved in Japan.
PHARMACOKINETICS

1. Healthy adults

(1) Single intravenous administration

To four healthy adult men, a single intravenous administration of 1,800 and 3,600 IU of epoetin beta (genetical recombination) was given, and the results [shifts in serum concentration, biological half-life (t1/2), blood concentration, area under the curve (AUC), and clearance (CL)] are shown below. Also, the cumulative urinary excretion over a 144-hour period was 2.4% and 4.6%, respectively.

Note 6): The approved dosage for intravenous use of EPOGIN is 6,000 IU (see the section on “DOSAGE AND ADMINISTRATION”).

<table>
<thead>
<tr>
<th>Parameters Following Single Intravenous Administration</th>
<th>1,800 IU</th>
<th>3,600 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2 (h)</td>
<td>3.3 ± 0.1</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>AUC (mIU·h/mL)</td>
<td>3,008.3 ± 316.8</td>
<td>5,279.2 ± 995.6</td>
</tr>
<tr>
<td>Vd (mL)</td>
<td>3,623 ± 243</td>
<td>6,277 ± 2,778</td>
</tr>
<tr>
<td>CL (mL/h)</td>
<td>758 ± 62</td>
<td>53.5 ± 140</td>
</tr>
</tbody>
</table>

Mean ± S.E.

(2) Single subcutaneous administration

Single subcutaneous doses of 1,500 and 3,000 IU of epoetin beta (genetical recombination) was administered to healthy adult males, and the results [shifts in serum concentration, maximum serum concentration (Cmax), and time before Cmax (tmax)] are shown below. Additionally, the cumulative urinary excretion over a 120-hour period was similar to that in the placebo group (urinary excretion of endogenous erythropoietin) for both doses.

Note 7): The approved adult dosages for subcutaneous use of EPOGIN are 6,000 to 12,000 IU (see the section on “DOSAGE AND ADMINISTRATION”).

<table>
<thead>
<tr>
<th>Parameters Following Single Subcutaneous Administration</th>
<th>1,500 IU</th>
<th>3,000 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mIU/mL)</td>
<td>21.1 ± 2.6</td>
<td>50.4 ± 9.0</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>12.8 ± 2.3</td>
<td>14.3 ± 0.7</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>31.2 ± 4.7</td>
<td>18.3 ± 1.5</td>
</tr>
<tr>
<td>AUC (mIU·h/mL)</td>
<td>1,059.4 ± 178.9</td>
<td>1,695.2 ± 231.8</td>
</tr>
<tr>
<td>F (%)</td>
<td>53.5 ± 9.0</td>
<td>41.8 ± 5.7</td>
</tr>
</tbody>
</table>

Mean ± S.E.

(3) Repeated subcutaneous administration

A subcutaneous dose of 1,500 IU of epoetin beta (genetical recombination) was administered 3 times at 5-day intervals to healthy adult males, and the results [shifts in serum concentration, Cmax, tmax, t1/2, AUC, F; AUCsc/AUCiv] after the first and the third administration are shown below. No changes were observed when the parameters following the third administration were compared to those following the first administration.

Note 8): The approved adult dosages for subcutaneous use of EPOGIN are 6,000 to 12,000 IU (see the section on “DOSAGE AND ADMINISTRATION”).

<table>
<thead>
<tr>
<th>Parameters Following Repeated Subcutaneous Administration</th>
<th>1st administration</th>
<th>3rd administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mIU/mL)</td>
<td>25.7 ± 4.3</td>
<td>23.3 ± 3.0</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>15.0 ± 0.0</td>
<td>16.5 ± 4.0</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>19.2 ± 3.5</td>
<td>23.8 ± 4.5</td>
</tr>
<tr>
<td>AUC (mIU·h/mL)</td>
<td>872.4 ± 116.4</td>
<td>888.3 ± 84.4</td>
</tr>
<tr>
<td>F (%)</td>
<td>44.1 ± 5.9</td>
<td>44.9 ± 4.3</td>
</tr>
</tbody>
</table>

Mean ± S.E.

CLINICAL STUDIES

These results were obtained using the lyophilized product.

1. Renal anemia in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (Subcutaneous administration)

Alleviation of renal anemia was observed, regardless of gender or age, in clinical studies conducted for patients with renal anemia undergoing continuous ambulatory peritoneal dialysis at 53 medical institutions throughout Japan. The efficacy rate was 87.5% (126/144 patients).

2. Renal anemia in patients prior to dialysis

(1) Intravenous administration

1) In double-blind comparative studies, the anemia-improvement rate, efficacy, and usefulness of EPO-
GIN were significantly superior to those of the placebo (p<0.001) [12].

2) Improvements in renal anemia were demonstrated, regardless of gender and age, in double-blind comparative and open clinical studies conducted at 115 medical institutions in Japan. The efficacy rate was 78.6% (136/173 patients).

2) Subcutaneous administration
1) In double-blind comparative studies, the efficacy rate (effective or better) of EPOGIN administered at a dose of 6,000 IU/week for 4 to 8 weeks to patients with renal anemia prior to dialysis was 90.2% (37/41 patients), significantly better than the placebo (p<0.001) [13].

2) Alleviation of renal anemia was observed, regardless of gender or age, in double-blind comparative and open clinical studies conducted for patients with renal anemia prior to dialysis at 83 medical institutions throughout Japan. The efficacy rate was 84.4% (238/282 patients).

3. Autologous blood donation of more than 800 mL to be stored for at least one week for a scheduled transfusion during surgery (Intravenous administration)
1) The results of placebo-controlled double-blind comparative studies showed that it was possible to collect about 1,200 mL of autologous blood with the administration of EPOGIN without significantly reducing hemoglobin concentration over a three-week period before surgery. The usefulness of EPOGIN was significantly superior to that of the placebo (P<0.001) [14, 15]. Also, it was shown that this treatment was helpful in saving or reducing the need for intra- and postoperative homologous blood transfusions [15].

2) In double-blind comparative and open clinical studies conducted at 128 medical institutions in Japan, the efficacy rate of EPOGIN was 88.2% (225 of 255 patients who were scheduled to undergo palliative surgery) regardless of gender, age, primary disease, or complications.

PHARMACOLOGY

1. Erythropoietic action
(1) In healthy rats and mice, epoetin beta (genetical recombination) increased reticulocyte counts, hemoglobin concentration, hematocrit, and red blood cell counts dose-dependently [16, 17].

(2) The administration of epoetin beta (genetical recombination) significantly improved anemia by increasing red blood cell counts in various animal models of renal anemia (5/6 nephrectomized rats [18], chronic nephritic rats [19], and renal failure dogs [20]).

(3) The hematopoietic effect of epoetin beta (genetical recombination) and human urinary erythropoietin were compared in healthy rats and 5/6 nephrectomized rats. The results showed no significant differences [17].

(4) In exsanguinated rats [21] and dogs [22, 23], epoetin beta (genetical recombination) suppressed the reduction of hemoglobin concentration and accelerated recovery.

(5) When epoetin beta (genetical recombination) was continuously administered to mice intravenously, the number of erythroid colony forming units (CFU-E) significantly increased in the bone marrow and spleen. The level of CFU-E (bone marrow) reached a peak in two days, but that of reticulocyte reached a peak in five days [24].

2. Mechanism of action
(1) It has been suggested that epoetin beta (genetical recombination) is a glycoprotein homopoietic factor having basically the same chemical structure as natural human urinary erythropoietin, and that it facilitates the differentiation and proliferation of the precursor cells of erythroblasts in the bone marrow into red blood cells. The bone marrow cells of mice were incubated with epoetin beta (genetical recombination), and their colony-forming abilities were measured. Even though epoetin beta (genetical recombination) stimulated the colony-forming unit of erythroid (CFU-E), the burst-forming unit of erythroid (BFU-E), and the colony-forming unit of megakaryocyte (CFU-Meg), it did not stimulate the colony-forming unit of granulocyte and macrophage (CFU-GM) at all (in vitro) [17].

PHYSICOCHEMISTRY

Nonproprietary name:
Epoetin Beta (Genetical Recombination) (JAN)

Composition:
Genetical recombinated human erythropoietin, produced in Chinese hamster ovary cells. A glycoprotein (molecular weight: ca. 30,000) consisting of 165 amino acid residues (C809H1301N229O240S5, molecular weight: 18,235.70).

PACKAGING
EPOGIN Injection Syringe 6000: Boxes of 1 and 10 syringes
EPOGIN Injection Ampoule 6000: Boxes of 1 and 10 ampoules

REFERENCES
9) Uji, Y. et al.: Shinryo To Shinyaku (Medical Consultation and New Remedies), 26(1), 1, 1989.

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Drug Information Center
Chugai Pharmaceutical Co., Ltd.
1-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo
103-8324, Japan
TEL: 0120-189706
FAX: 0120-189705
http://www.chugai-pharm.co.jp

Manufactured and Distributed by:
Chugai Pharmaceutical Co., Ltd., Roche group
1-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo
103-8324, Japan