



REPORT NUMBER 8

**Eporex and pure red cell aplasia.  
What should be MUHC policy for hemodialysis  
patients?**

**A Technology Assessment**

**By**

**The Technology Assessment Unit (TAU) of the  
McGill University Health Centre (MUHC)**

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## **Eporex and pure red cell aplasia. What should be MUHC policy for hemodialysis patients?**

### **Executive summary**

Erythropoietin is a natural hormone, mostly produced in the kidney. In advanced renal disease its production becomes deficient, and to prevent anemia it is necessary to replace it with administered recombinant human erythropoietin. Over the past 4 years reports have accumulated of the development of Pure Red Cell Aplasia (PRCA), a form of refractory anemia caused by the development of anti-erythropoietin antibodies in chronic renal failure patients receiving recombinant erythropoietin products. The preparation principally concerned is epoetin alfa (Eprex ®).

The reason for the development of anti-erythropoietin antibodies is unknown and is probably multifactorial. Thus far PRCA has only been reported in chronic renal failure patients; almost all have received Eprex by the subcutaneous (sc) route; there is a temporal relationship to the removal of the stabilizing agent, human serum albumin (HSA) from some preparations; there is the possibility that increased handling of the drug by individual patients may contribute to its developing increased immunogenicity; and the silicone used as lubricant of the syringes in which some Eprex preparations are dispensed has also come under some suspicion.

Although the incidence of PRCA is low (between 1/8,000 and 1/16,000 cases of antibody positive PRCA per year of exposure to Eprex sc in chronic renal failure cases), both the manufacturer and Health Canada now recommend that, whenever feasible, Eprex should be administered by the intravenous (iv) route. Until recently almost all hemodialysis patients at the MUHC have been receiving Eprex sc. There is, therefore, an urgent need to reconsider policy.

**In response to this need, there are two acceptable options available to the MUHC:**

- 1. Replace Eprex sc with Eprex iv.** The risk of PRCA associated with the *intravenous* use of Eprex appears to be virtually zero. There have been no confirmed cases of PRCA in patients who have received only intravenous Eprex after an estimated worldwide exposure of 560,500 patient years. Of these, 178,300 were between 1999 and 2002, the period during which Eprex

sc has been associated with an increased risk of PRCA. The medication can be given intravenously at the time of hemodialysis. *Elsewhere this policy has been widely, but not uniformly, adopted.*

**2. Replace Eprex sc by Aranesp.** Aranesp® or Darbepoetin which can be administered iv or sc, has also not yet been associated with any case of proven PRCA. It is included in the Québec list of covered medications under the drug insurance plan and if purchased by individual patients and self-administered sc there would be no added cost to the MUHC.

Aranesp was approved in Australia, Europe, and the USA in 2001 and in Canada in August 2002. There have now been approximately 80,000 patient years of exposure. Of these 65,000 have been in chronic renal failure patients, 44,000 by the sc route. The average patient exposure time is unknown but is probably close to six months. This is potentially important, as the median time to development of PRCA following exposure to Eprex sc has been estimated to be 9 months.

Therefore, while both Aranesp and Eprex iv appear to be safe based on the available evidence, the PRCA-free record of Eprex iv is more extensive and of longer duration. In addition, most patients strongly prefer having their medication administered intravenously during hemodialysis rather than administering it themselves subcutaneously.

## Recommendations

- 1) **Both Aranesp, and Eprex iv should be available options for MUHC patients.** The cost to the MUHC of either drug is comparable. When either drug is purchased through the Régime générale d'assurance médicament (RGAM) there is no additional cost to the MUHC. Both have acceptable profiles of efficacy and safety. *However, at the present time the evidence of safety of Eprex iv is based on a longer and more extensive experience.*

Other than in Québec this has led to a widespread, but not universal, adoption of Eprex iv as the option of choice. In Québec the intravenous administration of these medications constitutes a problem. This is because of a directive from the Ministry of Health to the effect that hospitals must pay for any medications they administer, even to outpatients.

If this directive were to be strictly observed, the in-hospital administration of iv Eprex would add approximately \$2 million to the annual costs of the MUHC. In order to remain budget neutral this would necessitate an equivalent reduction in hospital services. However, since patients up to this time have been purchasing their Eprex themselves through the RGAM, it may be possible to convince the Ministry to agree that the applicability of this directive to this particular case should be modified.

- 2) **Until this matter is clarified, all patients should continue to purchase their own medication, whether Eprex or Aranesp.** As a *short-term* policy, patients should bring their medication to hospital for administration during dialysis. As a corollary, these patients must be regularly instructed in the care of the medication.
- 3) **In order to regularize recommendation 2, the Ministry should urgently be requested to exclude the use of recombinant erythropoietin products used in the treatment of hemodialysis patients from their directive on the in-hospital administration of drugs.**
- 4) **In addition, the Ministry should be requested to revise the policy by which these medications are paid for through the RGAM, and to reinstitute a policy of their direct acquisition by, and reimbursement of their costs to, the hospitals.** To require patients to purchase their own medication and transport it to hospital for iv administration is not only inconvenient for patients, but runs the risk of medications being subjected to undue physical stress, thus increasing the risk of immunogenicity and adverse health outcomes.
- 5) **These policies should be kept under continual review by the physicians concerned and the Pharmacy and Therapeutics committee.** It must be remembered that the information available on this subject derives almost entirely from post marketing reports collected by the manufacturers. In spite of their best efforts the data must be considered fragile, and subject to change with the passage of time. Thus, policy revision will be necessary both in the light of new evidence and as a consequence of Ministerial policy decisions.

## **Eporex and pure red cell aplasia. What should be MUHC policy for hemodialysis patients?**

### **Introduction**

On January 29, 2003, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from Mr. V. Simon to consider the “Eprex/IV protocol” as a “priority project for the MUHC”. The Pharmacy and Therapeutics Committee had submitted a report to the MUHC entitled “Recombinant Epoetin Alpha and Pure Red Cell Aplasia” on September 25, 2002 [1]. This report forms the basis for the present document. However, new data are now available and a review of the evidence is appropriate. The Pharmacy and Therapeutics Committee is currently preparing a report on the use of Eprex in pre-dialysis and peritoneal dialysis patients. The present document will address the following question: *What should be the policy of the MUHC for hemodialysis patients in view of the newly reported risk of anemia associated with the use of Eprex?*

### **Method**

The association of anemia with the use of Eprex is a very recent discovery. Thus, the data to be reviewed are largely based on post-marketing reviews carried out by the manufacturer, and abstracts of presentations at scientific meetings. We have also received invaluable help from the additional Committee members and the Consultants listed on page 1. It is important to note that the data on which these recommendations are based are changing rapidly. Indeed, this has already necessitated one complete reformulation of the first draft of the report. *The conclusions are therefore not applicable over the long-term future without revision.*

### **Background.**

The development of red cells requires the natural hormone erythropoietin, which is produced mainly in the kidney. In advanced renal disease, failure to produce this hormone in adequate quantities results in refractory anemia. Until the development of recombinant human erythropoietin in 1988, this anemia was managed by administration of androgens (with very limited success) and repeated blood transfusion. For a review of the physiology and pharmacology of erythropoietin, see Fisher [2].

There are several recombinant erythropoietin preparations available worldwide. Recombinant Epoetin Alfa, Eprex®, (manufactured by Ortho Biotech, a subsidiary of Johnson and Johnson) became available in Canada in 1990, since which time it has been extensively used for the treatment of anemia in chronic renal failure patients. Because of its therapeutic benefit for such patients and its high cost, all Canadian provincial

governments initially paid for its acquisition through special funding arrangements. However in Québec, since the beginning of the "Régime générale d'assurance médicament" (RGAM) in 1998, patients have purchased their Eprex in their local pharmacies for subcutaneous administration in their homes. (However, many patients strongly resist administering their own injections and bring their medication into the dialysis Centre where it is given intravenously at the time of hemodialysis).

In February 2002 it was reported that a refractory anemia due to pure red-cell aplasia (PRCA) may occur in chronic renal failure patients during treatment with erythropoietin products. It appears to be caused by the development of neutralizing antibodies that act against both natural and recombinant erythropoietin [3]. PRCA is suspected when anemia in a chronic renal failure patient receiving erythropoietin products fails to respond to this medication. The diagnosis is confirmed by bone marrow biopsy, and the presence of neutralizing antierythropoietin antibodies in the serum (antibody +ve cases).

By September 30, 2002, 179 cases of suspected cases of PRCA had been reported, of which 112 were antibody +ve [4]. Two cases have been reported at the MUHC [5]. The majority of reports have been associated with the use of Eprex® (Epoetin alfa, Ortho Biotech/Janssen-Cilag) administered subcutaneously, and all but one has been in patients under treatment for chronic renal failure. Eprex was virtually the only erythropoietin product used until recently in Canada [4].

## **Eprex and PRCA**

*The cause* of the development of anti-erythropoietin antibodies in chronic renal failure patients receiving Eprex is unknown and probably multifactorial. There are several potential contributory factors:

- Route of administration. Antibody development in response to any immunogenic material is more likely to occur after subcutaneous than after intravenous exposure [6]. In animal studies another erythropoietin preparation, was found to develop antigenicity more frequently with subcutaneous than with intravenous use [7]. All Eprex associated cases of antibody +ve PRCA have followed subcutaneous administration [Ortho Biotech. 03].
- Human serum albumin (HSA). Until 1998 human serum albumin was used as a stabilizing agent. In that year, due to fear of contamination with Kreutzfeld prions it was removed from European formulations of Eprex and from the pre-filled syringes of Eprex available in Canada. The manufacturer states that there has subsequently been a decline in the stability of the HSA-free formulation when subjected to excess physical stress. The subsequent appearance of cases of PRCA coincides with this change [7]. However, two cases of PRCA have been reported in patients receiving subcutaneous HSA-containing formulations of Eprex.[8].

- Storage and handling. Eprex, like other protein substances is relatively unstable compared to other pharmaceutical products. Undue shaking or exposure to light or to temperatures outside the recommended range (2-8°C) may affect the integrity of the product and render it more immunogenic. There has been an increasing trend towards patient self-administration of Eprex sc in recent years and it is possible that the increased practice of purchasing and storing Eprex by individual patients may have resulted in increased immunogenicity [7].
- Silicone. Eprex pre-filled syringes also contain silicone, which is used as a lubricant for the barrel. Silicone is known to promote protein aggregation and thus to potentially increase immunogenicity. However, it is reported that current studies carried out by the manufacturer do not support the hypothesis that silicone has any causative role in PRCA [Ortho Biotech.03].

**The level of risk** of developing PRCA in chronic renal failure patients under treatment with Eprex sc is relatively low. Worldwide, by September 30, 2002, there had been 112 cases with documented anti-erythropoietin antibodies, associated with approximately 1,750,000 patient years of exposure, (an estimated risk of 1/15,625 patient years). Based on Canadian data the estimated risk would be 1/ 7,900 [Ortho Biotech.03]. It is unknown whether the higher risk of the latter estimate is due to chance, resulting from the smaller numbers involved, or is the result of more accurate post marketing reporting.

**Health advisories** have been issued in response to this risk. The manufacturer Janssen-Ortho, has recommended that “where feasible, Eprex should be administered intravenously to patients with CRF (chronic renal failure) while the Company investigates the cause of this adverse event”[7]. This advice has been reinforced by Health authorities in those countries in which Eprex is extensively used:

- Health Canada: “the product should be administered by the IV route in CRF patients (predialysis, hemodialysis and peritoneal dialysis), where feasible”[9].
- The UK Department of Health: “The subcutaneous route should not be used to administered Eprex to patients with chronic renal failure”[10].
- L’Agence Française de sécurité des Produits de Santé (Afssaps)[11] : “En décembre 2002, la réévaluation du profil de sécurité d’emploi d’ Eprex® par voie sous-cutanée chez les insuffisants rénale chronique a conduit l’Afssaps, après avis de la commission d’autorisation de mise sur le marché et en lien avec l’ensemble des Etats membres de l’union européenne, à contre-indiquer l’administration d’Eprex® par voie sous-cutanée chez les insuffisants rénaux chronique”.
- Janssen-Cilag, a Johnson and Johnson subsidiary, in consultation with Afssaps issued on December 2, 2002 an Urgent Safety Restriction to change its Summary of Product Characteristics for Eprex to further ensure intravenous administration when treating anemia in patients with chronic renal failure [12].



## MUHC Policy Options

In the light of these developments, Eprex can clearly no longer be administered by the subcutaneous route. Two theoretical options that have been considered are unfortunately not acceptable solutions. These are:

- **Replace Eprex sc by Epogen sc:** Epogen ® is a formulation of epoetin alfa manufactured in California by Amgen for use in hemodialysis patients in the USA. The manufacturer reports of that by December 30, 2002, only four cases of antibody positive PRCA had been identified after over 2.3 million patient years of exposure. Of these, two cases occurred after approximately 675,989 patient years of exposure to Epogen by the subcutaneous route [Amgen 03]. *Unfortunately, for apparently insurmountable legal and licensing reasons, this option is not available in Canada for the foreseeable future.*
- **Replace Eprex sc (from silicone containing syringes, HSA free) by Eprex sc (from vials free of silicone, containing HSA).** This was a recommended option of the Canadian Society of Nephrology in August 2002 [13]. However, although the risk of Eprex containing HSA sc may be lower, it is not zero. As of September 30, 2002, there had been three antibody positive cases of PRCA, although the Company is uncertain of the extent of exposure. In an update of 31 January 2003 the Canadian Society of Nephrology has changed its advice, and now "supports the recommendation that Eprex specifically should be administered via the IV route whenever feasible "[14]. Furthermore, such a policy would be contrary to the recommendations of the manufacturer, of Health Canada, and of other health authorities. *For these reasons this too is not an option.*

Two options remain:

- **Replace Eprex sc with Eprex iv.** By contrast with the risk of PRCA associated with the subcutaneous use of Eprex, the risk associated with intravenous Eprex appears to be virtually non-existent. There have been no confirmed cases of PRCA in patients who have received only intravenous Eprex after an estimated worldwide exposure of 560,500 patient years. Of these 178,300 were between 1999 and 2002, the period during which Eprex sc has been associated with an increased risk of PRCA [Ortho Biotech. 03]. Thus, the option of replacing Eprex sc with Eprex iv, employing multidose vials containing HSA, is supported by well-demonstrated evidence of safety. *Elsewhere, intravenous administration of Eprex has been widely adopted, and by September 2002 approximately 70-80% of chronic renal failure patients worldwide were already receiving Eprex intravenously [11].*
- **Replace Eprex sc by Aranesp.** Aranesp®, or Darbepoetin, which can be administered iv or sc, is also produced by Amgen, is available in Canada and is now included in the Québec list of covered medications under the drug insurance plan. The

estimated annual cost per patient of Aranesp, \$7,316, is slightly lower than that of Eprex \$8,301 (Appendix 1). The presently available preparation is HSA free. As of December 31st, 2002, this drug had not yet been associated with any proven case of PRCA [Amgen 03]. However, Aranesp is a relatively new medication, and its record of safety is less extensive than that of Eprex iv.

In the case of Eprex sc, the median duration from the start of use of the drug to the development of antibody mediated PRCA has been estimated to be nine months [Ortho Biotech 03]. Aranesp was approved in Australia in May and in Europe in June 2001, in the USA in September 2001, and in Canada in August 2002 [Amgen 03]. It is estimated by the Company that as of January 31, 2003, there have been approximately 80,000 patient years exposure to Aranesp, of which 65,000 have been in the context of chronic renal failure. In 44,000 of these the drug was administered sc. The overall average duration of exposure is unknown, but based on the number of patients involved and the total patient years of exposure [Amgen 03], is probably of the order of six months. In addition, in clinical trials, which commenced in December 1996 and involved 10,657 chronic renal failure patients, the exposure time averaged nine months [Amgen 03].

Thus, Aranesp is a drug that has not yet been associated with PRCA. If purchased by individual patients and self-administered sc, there would be no added cost to the MUHC. However, the total PRCA- free exposure of Aranesp sc is not yet as extensive as that of Eprex iv. In addition, there are patients who have become used, over the years, to having their medication administered at the time of hemodialysis, and many of these would strongly object to having to arrange for subcutaneous administration elsewhere. This issue is discussed below.

In summary, both Eprex iv and Aranesp sc or iv have a good safety record. While both should be available to MUHC patients, Eprex iv is the option with the best-demonstrated evidence of safety. *There are, however, problems related to the in-hospital administration of medications in Québec.*

### **Problems of In-hospital Administration of Medications in Québec.**

In Québec, a circular of the Deputy Minister of Health dated 2000-10-23 states that: "L'établissement doit assumer le coût des médicaments administrés sur place, dans le cadre d'activités prévues à son plan d'organisation, à même enveloppe budgétaire déjà allouée. Aucun frais ne pourront être exigés de l'utilisateur pour ces médicaments"[15]. This would appear to oblige hospitals that maintain dialysis centers to assume the cost of any medications administered, even to outpatients.

Thus, if patients were to receive in hospital the medication that they had purchased privately under the RGAM, the literal interpretation of this circular could result in an increase in MUHC annual costs of approximately \$2 million (Appendix 1). *This sum would be the equivalent of permanently closing between 14 to 15 acute medical beds.*

However, in view of the fact that patients have up to now paid for their own medication, the applicability of the abovementioned circular may be open to question. Furthermore, we are advised that the MUHC would not be contravening enacted legislation by following this option (B.Cappel. Personal communication). *Nevertheless, such a policy should be followed no longer than absolutely necessary.*

Accordingly, in order to avoid the reduction in services that would accompany strict application of the Ministerial directive concerning the in-hospital administration of drugs to outpatients, *the Ministry should be requested to exclude the use of recombinant erythropoietin products used in the treatment of hemodialysis patients from this directive.*

Meanwhile, in the short term until this is achieved, what options are available to enable the medication to be given intravenously without the MUHC incurring its cost?

- MUHC could request patients to continue to purchase their medication individually and to have it administered in their nearest CLSC. Although this would relieve the budget of the MUHC, the use of the arterio-venous fistula site even by skilled individuals, outside the hemodialysis unit might involve an increased risk of sepsis. Administration by venipuncture in the CLSC would avoid this risk, but such patients already have poor venous access, and what remains should be preserved. In addition, a weekly CLSC visit to receive an intravenous injection, for purely administrative reasons, would be an unreasonable burden to permanently add to the life of dialysis patients. *Accordingly, administration of medication by venipuncture in the CLSC, although possibly acceptable for very short-term use, is not an acceptable long term policy.*
- Patients could continue to procure their medication from their pharmacy and bring it into the dialysis center for intravenous administration. Patient instruction as to how to protect their medication from undue physical stress would be necessary[16]. *However, such a policy would be in contravention of the ministerial directive, and is only acceptable as a short term policy until the matter has been regulated with the Ministry.*

**It is recommended that both Aranesp and Eprex iv should be available at the MUHC.**

The costs to the MUHC are very similar. However, while both medications have a good safety record, *the evidence supporting the safety of Eprex iv is at present more extensive and of longer duration.* In addition, many patients are used to, and strongly prefer, receiving their medication at the time of hemodialysis rather than subcutaneously at home. It would seem to be completely inappropriate for this choice to be determined by a purely administrative directive. *Accordingly, the ministry should be requested to resolve the issue as rapidly as possible by exempting this medication from its directive[15].*

**In addition, the ministry should also be urgently requested to refund the cost of these medications directly to the hospitals as elsewhere in Canada, or alternatively to authorize the budget overrun that will result from application of present policy.**

To require patients to purchase their own medication for subsequent iv administration in hospital is not only inconvenient, but increases the risk of exposure of the medication to physical stresses which may increase its immunogenicity, and the risk of PRCA. *It is strongly recommended that a policy of, acquisition and preparation of the drugs by the hospital is the best option.*

**The conclusions arrived at in the present document should be repeatedly reviewed to make sure that they are consistent with contemporary information.**

Numerous factors including Ministerial responses to the two requests outlined above, and new information will necessitate revision of this policy. Furthermore, it must be remembered that the current information on which to base decisions on this subject derives almost completely from post-marketing reports collected by the manufacturers. In spite of their best efforts, these data must be considered fragile, and subject to change with the passage of time.

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We are grateful to Mrs Susan Wheeler of Ortho Biotech [Ortho Biotech 03], and to Mr V Paragamian of Amgen [Amgen 03] for their generous assistance in obtaining the most recent data on Eprex and Aranesp, respectively.

## Appendix 1

### Costs

#### Pharmacy Workload Costs

Based on the personnel required for Eprex dispensing prior to implementation of the RGAM in 1998, it is estimated that the pharmacy workload for dispensing Eprex would be: 0.5 Technical Assistants for each site (MGH,RVH), ie one Full Time equivalent Technical Assistant for the MUHC, plus 30% benefits = \$32,063.85 + \$9,618 = \$41,681 per year. (Analysis supplied by the Pharmacy of the MUHC).

#### Drug Acquisition Costs

**Eprex iv.** At the present time there are 251 hemodialysis patients under treatment at the MUHC.

The dose of Eprex varies from case to case. Assume an average dose of 10,000 units per patient per week.

The current cost to the MUHC is \$13.73 per 1000 units.

Annual acquisition cost of Eprex to MUHC =  $251 \times 10,000 \times 0.01375 \times 52 = \$1,794,650$

Assume 10% wastage + workload cost =  $\$1,794,650 + \$179,465 + \$41,681 = \$2,015,796$

**Aranesp sc.** Assume that the dose of Aranesp (ugm) is the equivalent of the total weekly dose of Eprex (10,000 units), divided by 200 = 50 ugm / week.(Dr S Prichard, Nephrology division, MUHC)

The cost of Aranesp = \$140.7 per 50 ugm syringe.(A Bonnici,Pharmacy,MUHC)

Annual acquisition cost of Aranesp =  $251 \text{ patients} \times \$140.70 \times 52 \text{ weeks} = \$1,836,416.$

This would not be a charge to the MUHC unless administered in hospital at the time of hemodialysis.

NOTE: Neither of the above estimates allow for the possibility that the dose may be underestimated.