Practice guidelines on the use of erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anemia

L. Dirix, A. Awada, D. Bron, J.-L. Canon, J. De Grève, Y. Humblet, M. Peeters, S. Van Belle, J. Vansteenkiste, J. Vermorken

Summary

On July 1st 2009, a panel of experts met with the goal to provide a joint medical opinion on the use of erythropoiesis-stimulating agents (ESAs) in chemotherapy-induced anemia (CIA), as well as a joint proposal for revised reimbursement criteria in Belgium. The goal is to provide a clear and workable guidance on the use of ESAs in their registered indication: chemotherapy induced anemia in cancer patients. An overview of participating experts can be found in *Table 1*.

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Short minutes of the meeting

In a first presentation, professor Yves Beguin (CHU Sart Tillman, Liège) gave an overview of the benefits of treatment with erythropoiesis-stimulating agents (ESAs) in terms of reduction of the need for transfusions and increase in quality of life, as well as on the different possible dosage schedules with different products (thrice weekly (TIW), once weekly (QW), once every 3 weeks (Q3W)) and the demonstration that dose doubling (2x standard dose) did not provide a better response for patients initially not responding to standard doses. He went through the pivotal trials that led to the original registrations of each product. He clarified that on average, two thirds of patients seem to respond to therapy. (In the later discussion on how many patients do finally benefit from treatment with ESA, agreement was reached that for patients starting ESA treatment, red blood cell (RBC) transfusion can be completely avoided for an additional ±30% of patients compared to the control groups.) Two factors seem responsible for a possible lack of response: inflammation and/or functional iron deficiency. Inflammation was shown to lead to decreasing Hb levels, and correction of functional iron deficiency with iron sucrose 200-300 mg IV Q2W x 3 doses has shown to lead to a faster response, higher response rate, fewer transfusions and less ESA use compared to patients not receiving IV iron, with 5 clinical studies demonstrating the positive effect of the addition of IV iron in these

Authors: L. Dirix[1], A. Awada[2], Y. Beguin,[3] D. Bron[4], J.-L. Canon[5], J. de Grève[6], Y. Humblet[7], M. Peeters[8], S. Van Belle[9], J. Vansteenkiste[10], J. Vermorken[11], [1]Iridium Cancer Network, Antwerpen (medical oncology), [2]Institut Bordet, Brussels (medical oncology), [3]CHU Sart Tilman, Liège (hematology), [4]Institut Bordet, Brussels (hematology), [5]GHdC, Charleroi (onco-hematology), [6]UZ Brussels (medical oncology), [7]University Hospital St. Luc, Woluwe (medical oncology), [8]UZ Gent (digestive oncology), [9]UZ Gent (medical oncology), [10]UZ Leuven, campus Gasthuisberg (pulmonary oncology), [11]UZ Antwerpen (medical oncology)

Please send all correspondence to: Dr. L. Dirix, Oncologisch Centrum GVA, Sint-Augustinusziekenhuis, Oosterveldlaan 24, 2610 Wilrijk, Belgium, tel: 0032 3 443 30 11, e-mail: luc.dirix@gza.be

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Table 1. List of experts that participated at the consensus meeting

Dr. Ahmad Awada	Institut Bordet - Brussels (medical oncology)
Prof. Yves Beguin	CHU Sart Tilman - Liège (hematology)
Prof. Dominique Bron	Institut Bordet - Brussels (hematology)
Dr. Jean-Luc Canon	GHdC - Charleroi (onco-hematology)
Prof. Jacques De Grève	UZ Brussels (medical oncology)
Dr. Luc Dirix	Iridium Cancer Network - Antwerpen (medical oncology)
Prof. Yves Humblet	Hop. Univ. St Luc - Woluwe (medical oncology)
Prof. Marc Peeters	UZ Gent (digestive oncology)
Prof. Simon Van Belle	UZ Gent (medical oncology)
Prof. Johan Vansteenkiste	UZ Gasthuisberg - Leuven (pulmonary oncology)
Prof. Jan B. Vermorken	UZ Antwerpen (medical oncology)

patients. On the topic of safety of these agents, professor Beguin mentioned the trend of increased hypertension (mostly however observed in the chronic kidney disease (CKD) patients), increased risk of thrombotic events and the lack of any evidence for tumour growth. On the long term safety in terms of overall survival (OS) or progression free survival (PFS), an exhaustive number of studies was discussed, starting with the study of Littlewood et al. that, in 2001, published results that seemed to demonstrate a trend towards increased overall survival for patients receiving epoetin alpha versus the control group. This study led to several other studies trying to confirm such finding in different settings of anemia in cancer patients, with very different and sometimes conflicting outcomes.

Results from several studies in Head and Neck cancer (s.a. ENHANCE, DAHANCA, RTOG-99-03) in patients treated with radiotherapy and given ESAs with the aim to increase Hb levels to sometimes as high as 14-15 g/dl, found a clear detrimental effect on local control and overall survival for the group treated with ESAs. Also in a study in patients with cervical cancer receiving both chemotherapy and radiotherapy as their cancer treatment, the ESA treated groups did worse than the control group. This lead to professor Beguin's conclusion that ESAs are clearly not indicated for use in patients receiving radiotherapy only.

In lymphoid tumours, a study by Hedenus et al. in a mixed tumour setting of several lymphoid malignancies showed a worse outcome on OS but identical PFS. Large studies in diffuse large B-cell lymphoma (DLBCL) (LNH03-6B) and Hodgkin's disease (GHSG-H15) and a smaller study in (acute) lymphoblastic lymphoma/Burkitt's lymphoma (ALL-LL-BL) (Mattiuzzi) showed no significant differences in outcome. The conclusion seems to be that in lymphoid tumours results should be considered as neutral.

In breast cancer, conflicting results were recorded in different studies. A study published by Leyland-Jones et al. in 2005 (BEST) in metastatic breast cancer and the preliminary results of the PREPARE study in neo-adjuvant setting presented by Untch reported a worse outcome for ESA-treated patients, whereas other studies such as reported by Aapro et al. in 2008 (BRAVE), Chang et al. in 2005 (EPO-CAN-17) and Moebus et al. in 2007 did not find any outcome difference in terms of OS or PFS.

Also in non-small cell lung cancer (NSCLC), conflicting results were reported: a study by Wright et al. 2007 (EPO-CAN-20) in the setting of metastatic lung cancer reported worse outcome, and another study (EPO-GER-22) reported no significant differences. In SCLC, the 2 studies reporting outcomes: (N93-004) by Grote 2005 and (2001-0145) by Pirker 2008 reported no significant differences in OS, with completely overlapping survival curves.

In the setting of anemia of cancer (without any chemotherapy or radiotherapy), a study by Smith et al.

Table 2. Comparison of current erythropoiesis-stimulating agent (ESA) labels and guidelines.

	EU Label EMEA/CHMP	EORTC Guidelines	ESMO Guidelines	ASCO/ASH Guidelines	US Label FDA
Initiation of ESA	symptomatic anemia (eg. Hb ≤10 g/dl)	Hb 9-11 g/dl based on anemia-related symptoms	Hb ≤10 g/dl	approaching or has fallen below 10 g/dl	Hb ≤10 g/dl
Mild anemia?	-	may be considered in selected asymptomatic patients, Hb 11-11.9 g/dl to prevent further decline	Hb 10-12.0 g/dl, treatment can be considered in case of symptoms	Hb 10-12 g/dl, start determined by clinical circumstances	declining Hb <12, decision to use epo or wait until <10 should be determined by clinical circumstances
Target Hb	10-12 g/dl, A sustained Hb >12 g/dl should be avoided	about 12 g/dl	Hb should not exceed 12 g/dl	near 12 g/dl	Hb exceeding level needed to avoid transfusion
Non-responders?	epo A+B: doule dose if <1 g/dl in 4 weeks, if <1 g after 8 weeks: discontinue, darbepoetin: dose doubling not recommended, if no clinical response after 9 weeks, discontinue	'no recommendation that dose escalation should be general approach'	dose doubling. Continuation beyond 6-8 weeks in the absence of response is not beneficial	dose escalations as per label. Discontinue if no response after 6-8 weeks	discontinue if no response after 8 weeks or if transfusions still required
Dose adjustments	- if Hb >2g/m or >12 g/dl → reduce by 25 or 50% - if Hb >13 g/dl → discontinue and restart until <12 g/dl	individualize treatment when reaching target (increasing dose interval or titration to lowest effective maintenance dose	= idem EU label	dose reductions as per label and recommended when Hb rise >1 g/2w or exceeds 11 g/dl	- if Hb >1 g/2w or >12 or 11 g/dl → reduce by 25 or 40% - if Hb >12 g/dl → discontinue and restart until <11 g/dl, restart at lower dose
Iron		evidence for IV iron when iron depleted IV iron to be reserved for patients with absolute or functional iron deficiency	iv iron substitution when iron deficiency	iron repletion is indicated	iron therapy recommended if serum ferritin <100 mcg/L or serum transferrin saturation <20%
Safety	4.4 Special warnings and precautions:….. "… in some clinical situations blood transfusion should be the preferred treatment for management of anemia in patients with cancer. The decision to use ESA should be based on a benefit-risk assessment, …" Including factors, such as type of tumour, stage, degree of anemia, life-expectancy, environment and patients preference.	increased risk: TE events x 1.6 and hypertension	Decreased survival or PFS seen in several randomized studies but design aimed at Hb >12 g/dl and included patients with baseline Hb >10 g/dl TE: risk increased by 67%. Use to be carefully considered in patients at high TE risk … In patients treated with curative intent, ESAs should be used with caution. (D)	complete section on discussion of individual trials and ODAC briefings 2004 and 2007	Boxed Warning: - ESAs shortened OS or PFS in some studies … - use lowest dose needed - use only for anemia due to chemotherapy - ESA not indicated when the anticipated outcome is cure - discontinue following completion of a chemo course

EMEA=European Medicines Agency, CHMP=Committee for Medicinal Products for Human Use, FDA=Food and Drug Administration, OS=overall survival, PFS=progression-free survival.

(2001-0103) reported a worse outcome on OS for ESA-treated patients, confirming former results of a study published by Wright et al. (2007), and demonstrating that ESAs should not be used in the 'anemia of cancer' (AoC) setting.

After shortly demonstrating the relationship between Hb levels and QoL improvements and the effectiveness of ESAs in reducing the need for RBC transfusions, Professor Vansteenkiste (UZ Leuven, campus Gasthuisberg) presented a schematic analysis of the different meta-analyses as published by Bohlius et al. in 2005, 2006 and 2009. In the first meta-analysis, published in 2005, and comprising trials that studied the treatment of CIA, a significant positive effect of ESAs on OS with a hazard ratio (HR)=0.81 (0.67-0.99) was reported. With the observation of the proven benefit of ESAs in treatment of CIA, and the observation that anemia is a negative prognostic factor, the hypothesis was generated that prevention of anemia would improve prognosis, and several studies were set up in different settings: prevention of anemia during chemotherapy ('high Hb studies'), prevention of anemia during radiotherapy ('RT'-studies) and studies on normalization of anemia in patients not receiving chemotherapy ('AoC'-studies). In the most recent pharmacovigilance update (2008) 8 out of 59 RCTs gave rise to some safety concern; 4 in 'high Hb' setting (BEST, PREPARE, Thomas et al., Hedenus et al.), 2 'AoC' studies (Wright et al., Smith et al.) and 2 RT studies (Henke et al., Dahanka et al.). The second meta-analysis published by Bohlius et al. in 2006 therefore comprised a mixture of studies in both treatment as well as prevention of anemia in different settings (not only CIA), and the HR for OS turned towards 1.08 (0.99-1.18) in the disadvantage of ESA-treated patients. Interesting to note that for the studies performed between 2002 and 2005, the HR was reported to be 1.16. In the most recent, patient level meta-analysis for studies in chemotherapy-induced anemia (CIA), still mixing the treatment and prevention approaches, the HR for OS became 1.04 (0.97-1.11), with most recent trials again responsible for the more negative outcomes as demonstrated by the subgroup analysis published by Bohlius et al. (HR for mortality-on-study in all chemotherapy treated patients was 1.10 (0.98-1.24) compared to a HR for mortality for all patients (including patients treated with RT-only and those with AoC) of 1.17 (1.06-1.30).
A very recent patient level meta-analysis on all 7 double-blind, placebo-controlled RCTs with darbepoetin for the treatment of CIA, Ludwig et al. (2009) reported completely overlapping curves for both OS as well as PFS for ESA-treated and control group.
In summary, professor Vansteenkiste concluded that in his opinion the safety signals in terms of outcome reported for the settings of AoC, RT and prevention or high Hb-level studies should clearly lead to the abandoning of use of ESAs in those particular settings, whereas meta-analysis results and individual studies seem to clearly confirm a positive risk/benefit in the registered indication of 'treatment of CIA', where a proven benefit for the use of ESAs in terms of reduction of RBC transfusions and a better QoL has also been demonstrated.

The different safety signals from individual studies, as well as the meta-analysis results have been discussed in specific hearings by Oncologic Drugs Advisory Committee (ODAC) in the US and by European Medicines Evaluation Agency (EMEA) in Europe. As a result, the labels of the different ESA-products have been updated with appropriately revised dosage recommendations and warnings covering the different safety signals observed.
Also international guidelines such as the ESMO, EORTC and ASH/ASCO practice guidelines on the use of ESAs have updated their practice guidelines following the availability of new data on the use of ESAs (*Table 2*).

In a third presentation of the evening, professor Van Belle (UZ Gent) presented the current Belgian reimbursement criteria in a historic perspective. In the current setting, very different criteria are used depending on if the chemotherapy includes a platinum compound or not. For platinum-based chemotherapy settings, the current criteria are very unrestrictive, as there is no definition of initiation minimal Hb level, nor dosage or duration limitations for the use of ESAs in this setting. For non-platinum based chemotherapy on the other hand, starting and stopping rules have been established, although these criteria were not evidence based. In current practice, ESA therapy can be initiated for chemotherapy-treated patients for whom the Hb level has dropped below 11 g/dl in a first starting therapy for

Table 3. Current reimbursement criteria in onco-hemato: **platinum based chemotherapy**.

Eprex®/Binocrit®	NeoRecommon®	Aranesp®
Treatment of secondary anemia induced by platinum CT in adult cancer patients	Treatment of secondary anemia induced by platinum CT in adult patients with solid tumours	Treatment of secondary anemia induced by platinum CT in adult cancer patients
• Exclusion of other causes of anemia (occult hemorrhage, iron deficiency, hemolysis, …) • Need for upfront demand to medical advisor • Reimbursement given for 12 months after authorization of medical advisor • Possibility of prolongation for 12 months → No specific criteria regarding initial Hb level, dose, duration of treatment, … → Doubling of dose allowed if the increase in hemoglobin is inadequate		

Table 4. Current reimbursement criteria in onco-hemato: **non-platinum based chemotherapy**.

	Eprex®/Binocrit®	NeoRecommon®	Aranesp®
• Secondary anemia patients with solid or hematological tumours treated with CT • Hb level <11g/dl • Exclusion of all others of anemia			
Initial treatment	Dose: 150 IU/kg 3x/week or 450 IU/kg per week	Dose: 450 IU/kg per week	Dose: 2.25 µg/kg per week
Duration: 4 weeks for solid tumours; 8 weeks for hematological tumours			
If increase in Hb level ≥1 g/dl without any transfusion after initial treatment ⇓			
Continuation of treatment = 8 weeks	Dose: 150 IU/kg 3x/week or 450IU/kg per week	Dose: 450 IU/kg per week	Dose: 2.25 µg/kg per week
• No need for upfront demand to medical advisor • Keep all information (tumour type, chemotherapy, Hb level, …) at disposition of medical advisor • Reimbursement maximum 2x per 12 months			

4 weeks for solid tumours, and 8 weeks for hematological tumours. If a Hb response of at least 1 g/dl has been observed within these first 4 (or 8) weeks, a further 8 weeks of therapy can be reimbursed (*Table 3* and *4*).

Consensus statement

After the exhaustive review of individual studies reporting on long term safety, the data of the different meta-analyses and the updated labels, guidelines as well as current reimbursement criteria, the scene was set to open the debate aiming to arrive at a common medical opinion by the expert-panel on the practical use of ESAs in CIA.

The topics suggested for discussion included the following:

- How many and which patients are obtaining benefit?
- When should ESA therapy be initiated?
- Do we need to make a distinction between platinum and non-platinum based chemotherapy?
- Which target Hb level to aim for?
- How long needed to evaluate if patient is responder or not? And how to define response?
- Treatment duration? When stop treatment?
- What about dose increases (e.g. dose-doubling) if no response after initial treatment?
- What about iron repletion guidelines?
- What is our advice concerning the potential treatment in an adjuvant or curative setting?

De specialiteit X (hier Aranesp) wordt vergoed als ze is voorgeschreven door de geneesheerspecialist die verantwoordelijk is voor de behandeling en wordt toegediend als ondersteunende therapie bij rechthebbenden, die op het ogenblik van de aanvraag met een anti-neoplastische chemotherapie worden behandeld, een symptomatische anemie vertonen en waarbij het hemoglobinegehalte gedaald is onder de 11 g/dl (6,87 mmol/l) en na het uitsluiten en behandelen van andere oorzaken van anemie, in één van de volgende doses:

a) **in een aanvangsbehandeling:**
een weekdosis van 2,25 µg/kg lichaamsgewicht gedurende een initiële behandelingsperiode van maximum 8 weken; *(aanpassen relevante doses voor epo a en b)*

b) **in een consolidatiebehandeling:**
als na de aanvangsbehandeling zonder tussentijdse transfusie het hemoglobinegehalte met minimum 1 g/dl (0,6245 mmol/l) ten opzichte van de beginsituatie gestegen is, kan een verlenging van de vergoeding van de behandeling toegekend worden. De behandeling met deze specialiteit zal de duur van de verdere chemotherapie met maximaal 4 weken overschrijden.

De behandeling zal erop gericht zijn een maximale Hb-waarde van ongeveer 12 g niet te overschrijden, en dient onderbroken indien een waarde van 13 g/dl of een blijvende waarde boven 12 g/dl zou bekomen worden.
Het verhogen van de gemiddelde weekdosis bepaald in de aanvangsbehandeling is niet toegestaan.

De bewijsstukken die aantonen dat aan de voorwaarden is voldaan en waarin uitdrukkelijk het type tumor, de toegediende anti-neoplastische behandeling, het hemoglobinegehalte en in het geval van een consolidatiebehandeling, het hemoglobinegehalte bij start en na 8 weken behandeling met deze specialiteit vermeld zijn, moeten door de voorschrijvende arts ter beschikking worden gehouden van de adviserend geneesheer.
De machtiging tot vergoeding in deze indicatie kan maximaal 2 maal per 12 maanden verleend worden.

Figure 1. Proposed text for reimbursement criteria, Dutch version.

After ample discussion on these topics, and initially hearing several interpretations and points of view, the expert panel came to the following consensus statement:

ESAs should be used within their approved label, meaning, for treatment of CIA, not for prevention neither for anemia of cancer nor in radiotherapy-only-treated patients.

Within the setting of CIA:

- ESA treatment can be initiated in a patient showing symptomatic anemia and an Hb level that has fallen to at least below 11 g/dl. (**symptomatic anemia, <11 g/dl**)
- The maximal Hb level should be around 12 g/dl. (**maximum = around 12 g/dl**)
- If Hb level reaches above 13 g/dl or continuously remains higher than 12, treatment should be discontinued, and only reinstated at adequately reduced doses after the Hb level has lowered to below 12 g/dl. (**discontinue if above 13 or continuously above 12**)
- ESAs, once started, should be given for an initial treatment period of 6-8 weeks, after which response should be evaluated. For patients considered responders (obtaining a rise in Hb value of at least 1 g/dl after 8 weeks), treatment can be further continued as needed until maximum 4 weeks after the last chemotherapy administration. For non-responders (patients not reaching 1 g/dl increase of Hb after 8 weeks), treatment should be stopped (a former practice of increasing the ESA dosages for patients not responding after an initial 8 weeks of ESA at standard dosage was not considered good practice, as data did demonstrate no benefit by doing so). (**Initial treatment for 6-8 weeks, evaluate response, no response = stop treatment, responder: continue if needed until a maximum of 4 weeks after last chemotherapy administration**).
- It should be routine practice to evaluate iron deficiency in patients considered for ESA treatment by measuring transferrin saturation (Tsat) at baseline and during treatment. In case of a

La spécialité X (ici Aranesp) est remboursée si elle est prescrite par le médecin spécialiste responsable du traitement et administrée comme thérapie de soutien chez des bénéficiaires qui, au moment de la demande, sont traités avec une chimiothérapie antinéoplasique, ont une anémie symptomatique et chez lesquels le taux d'hémoglobine a diminué en dessous de 11 g/dl (6,87 mmol/l), après exclusion et traitement d'autres causes d'anémie, en une des doses suivantes:

a) en cas de traitement initial:
une dose hebdomadaire de 2,25 µg/kg poids corporel pour une période de traitement de maximum 8 semaines; *(adaptez dosages pour epo a et b)*

b) en cas de traitement de consolidation:
si après le traitement initial, sans transfusion intermédiaire, le taux d'hémoglobine a augmenté d'au minimum 1 g/dl (0,6245 mmol/l) par rapport à la situation de départ, une prolongation de remboursement du traitement peut être accordée. Le traitement avec cette spécialité ne pourra être continué plus de 4 semaines après la dernière administration de la chimiothérapie.

Le traitement aura comme objectif de ne pas dépasser un taux maximal d'hémoglobine aux alentours de 12 g/dl et doit être interrompu si le taux d'hémoglobine atteint 13 ou reste constamment au dessus de 12 g/dl.
Une augmentation de la dose par semaine, comme décrit pour le traitement initial, n'est pas permise.

Les pièces justificatives démontrant que les conditions sont rencontrées et dans lesquelles le type de tumeur, le traitement antinéoplasique administré, le taux d'hémoglobine et, en cas de traitement de consolidation, le taux d'hémoglobine au début et après 8 semaines de traitement avec cette spécialité sont formellement mentionnés, doivent être tenues par le médecin prescripteur à la disposition du médecin-conseil.
L'autorisation de remboursement dans cette indication peut être accordée au maximum 2 fois par 12 mois.

Figure 2. Proposed text for reimbursement criteria, French version.

Tsat below 20%, IV iron supplementation should be administered together with ESA treatment, and Tsat monitored during the further treatment. (**Evaluate iron status by Tsat, if Tsat <20% → IV iron sucrose supplementation: 200-300 mg IV over 1 h Q2W x 3 doses**). This practice has been shown in 5 separate studies to lead to faster response, increased response rate, a further reduction of the need for RBC transfusions and a lower total dosage of ESA needed to sustain an adequate Hb level.

- The panel discussed in depth about their concerns regarding the potential negative impact on survival from the use of ESAs in curative settings, and agrees with the most recent recommendations by EMEA that state the following: *"In view of the above, in some clinical situations blood transfusions should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on the benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference."* (EU-label texts)

Observing the results of this expert consensus, these guidelines are in practice very similar to the ESMO recommendations.

Reimbursement proposal

In order to enable the Belgian physicians to apply above practice guidelines in a correct manner and with the aim to both simplify criteria as well as avoid criteria that would enable a use larger than the one recommended (see current criteria for platinum-treated patients), the panel **proposes the following criteria to be implemented for Belgian reimbursement of ESAs**:

- Eligible patient: **symptomatic** CIA **and** with a **Hb level <11 g/dl**.
- Prior exclusion and correction of all other causes

Key messages for clinical practice

1. **Within the setting of chemotherapy-induced anemia, erythropoiesis-stimulating agents (ESAs) should be:**
   - **Initiated with symptomatic anemia, Hb levels <11 g/dl**
   - **The maximum Hb level should be around 12 g/dl**
   - **Discontinued if above Hb level 13 or continuously above 12**

2. **Initial ESA treatment should be given for 6-8 weeks after which response should be evaluated**
   - **No response = stop treatment**
   - **Responder: continue if needed until a maximum of 4 weeks after last chemotherapy administration**

3. **Iron status should be evaluated by Tsat. If Tsat <20% → IV iron sucrose supplementation: 200-300 mg IV over 1 h Q2W x 3 doses.**

of anemia.

- No more distinction in criteria between different types of chemotherapy regimens nor tumour types (solid or hematological tumours/platinum or non-platinum regimens).
- Initial treatment: 8 weeks.
- Evaluation of response after maximum 8 weeks:
  - If Hb level increased less than 1 g/dl → STOP ESA
  - If Hb level increased with 1 g/dl or more: continue further ESA therapy if needed, with a maximal duration of 4 weeks after last chemotherapy administration.
- The maximal Hb level should be around 12 g/dl.
- No dosage increase versus standard dose allowed. (standard dosages in equivalents per week mentioned in detailed texts for reimbursement)
- Treatment needs to be discontinued if Hb above 13 or continuously above 12, and reinstated when needed.
- Dosages and dosage reductions as per most recent labels.
- Iron status of the patient should be monitored at initiation and during treatment.
  If Tsat <20%: Replenishment by IV administration of iron sucrose needs to be added to the ESA treatment.

An example of (draft) text for reimbursement criteria (French and Dutch version) is represented in *Figures 1* and *2* on page 62 and *63*.