HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
29 October 2014

ETHYOL 50 mg/ml, powder for solution for infusion
Box of 3 vials of 500 mg (CIP: 34009 558 450 8 9)

Applicant: BIOPROJET PHARMA

INN	Amifostine
ATC Code (2014)	V03AF05 (cytoprotective agent)

Reason for the review	**Re-assessment of the IAB following joint referral by the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services on 10 October 2013, and in accordance with article R 163-19 of the French Social Security Code.**
List concerned	**Hospital use (French Public Health Code L.5123-2)**
Indication(s) concerned	▪ **"Chemotherapy:** - **Prevention of the risk of neutropenia and its consequences (in particular, infections) due to the combined use of cyclophosphamide and cisplatin in patients with advanced ovarian cancer (FIGO stage III or IV).** - **Prevention of the cumulative renal toxicity of cisplatin and treatments including cisplatin when the unit dose thereof is between 60 and 120 mg/m^2, in combination with measures to ensure adequate hydration in patients with advanced solid non-germinal tumours.** ▪ **Radiotherapy:** - **Prevention of acute and late xerostomia in ENT cancers, in combination with standard fractionated radiotherapy."**

Actual Benefit	**Insufficient**
Improvement in Actual Benefit	**N/A**
Therapeutic use	**Amifostine no longer has a role in the therapeutic strategy:** - **in the prevention of neutropenia in patients with advanced ovarian cancer treated with cyclophosphamide and cisplatin** - **in the prevention of the cumulative renal toxicity of cisplatin** - **in the prevention of acute or late xerostomia in ENT cancers treated by standard fractionated radiotherapy**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	17 February 1995 (mutual recognition)
Prescribing and dispensing conditions /special status	List I

ATC Classification	2014	
	V	Various
	V03	All other therapeutic products
	V03A	All other therapeutic products
	V03AF	Detoxifying agents for antineoplastic treatment
	V03AF05	Amifostine

02 BACKGROUND AND PURPOSE OF THE RE-ASSESSMENT

As part of the work aimed at updating the list of chargeable medicinal products in addition to hospital services provided by the Hospitalisation council, and pursuant to article R 163-19 of the French Social Security Code, the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services has applied to HAS for a ruling on the IAB of proprietary medicinal products, including **ETHYOL 50 mg/ml, powder for solution for infusion**, the subject of this opinion. Due to the length of time since inclusion, which took place before the IAB formed part of the assessment, as it does today, this criterion had not been assessed by the Committee.
As the company has requested the deletion of the presentation in 375 mg vials, this opinion only related to the presentation in 500 mg vials.

02.1 Summary of previous assessments

Date of Opinion (reason for the review)	12 April and 13 May 1995 (1st request for approval for hospital use)
Indication	"Prevention of the risk of neutropenia and its consequences (in particular, infections) due to the combined use of cyclophospohamide and cisplatin in patients with advanced ovarian cancer (FIGO stage III or IV)."
Actual Benefit	Not applicable.
Improvement in Actual Benefit	Within the framework of the current therapeutic strategy, limited sole benefit in neutropenia in stage III or IV ovarian cancer treated by moderately neutropenia-inducing chemotherapy (cisplatin and cyclophosphamide), this product offers a moderate clinical contribution of level III, taking into account its level of efficacy and the adverse effects linked to its use. However, ETHYOL has cytoprotective potentials which, if demonstrated clinically, would extend its therapeutic benefit beyond the present level.
Comment	The Committee stresses the poor nature and shortcomings of the dossier supplied by the company. However, because of the nature of the disease concerned, the competence of the rapporteur in the treatment of ovarian cancer, as well as the knowledge of the participants in the meeting, the Committee nevertheless proceeded with the assessment of this new medicine.

Date of Opinion	24 September 1997 (extension of indication)
Indication	"Prevention of the cumulative renal toxicity of cisplatin and treatments containing cisplatin when the unit dose thereof is between 60 and 120 mg/m^2, in combination with measures to ensure adequate hydration in patients with advanced solid non-germinal tumours."
Actual Benefit	Amifostine has been shown to be effective in the prevention of the cumulative renal toxicity of cisplatin, and is moderately safe. There is no alternative treatment. Amifostine has an appreciable place in the prevention of the cumulative renal toxicity of cisplatin and of treatments including cisplatin in patients with advanced solid non-germinal tumours.
Improvement in Actual Benefit	ETHYOL displays a moderate clinical benefit in the therapeutic strategy of treatment with cisplatin, taking into account its level of efficacy and the undesirable effects linked to its use.

Date of Opinion (reason for the review)	1 March 2000 (extension of indication)
Indication	"Prevention of acute and late xerostomia in ENT cancers, in combination with standard fractionated radiotherapy."
Actual Benefit	Acute or late xerostomia is an extremely common (4 patients out of 5) side effect of the treatment of ENT cancers by radiotherapy. It may compromise the continuation of treatment and its effects (digestive, phonation) may lead to a marked deterioration in the quality of life. This proprietary medicinal product is intended as preventive therapy. The efficacy/adverse effects ratio in this indication is modest. There is no alternative treatment. The actual benefit of this proprietary medicinal product in this indication is substantial.
Improvement in Actual Benefit	Taking into account its efficacy/safety ratio and the absence of an alternative, ETHYOL provides a moderate improvement in actual benefit in the therapeutic strategy for the prevention of acute and late xerostomia in ENT cancers in combination with standard fractionated radiotherapy.

03 THERAPEUTIC INDICATIONS

- "Chemotherapy:

- Prevention of the risk of neutropenia and its consequences (in particular, infections) due to the combined use of cyclophosphamide and cisplatin in patients with advanced ovarian cancer (FIGO stage III or IV).
- Prevention of the cumulative renal toxicity of cisplatin and treatments including cisplatin when the unit dose thereof is between 60 and 120 mg/m^2, in combination with measures to ensure adequate hydration in patients with advanced solid non-germinal tumours.

- Radiotherapy:

- Prevention of acute and late xerostomia in ENT cancers, in combination with standard fractionated radiotherapy."

04 DOSAGE

"ETHYOL must not be used except under the supervision of physicians experienced in cancer chemotherapy or radiotherapy.

- Chemotherapy:

In patients with advanced ovarian cancer receiving treatment with a combination of cisplatin and cyclophosphamide, the recommended initial dose of ETHYOL is 910 mg/m^2, administered once daily as an IV infusion over 15 minutes starting during the 30 minutes preceding the chemotherapy based on products administered by short infusions.

When ETHYOL is administered with the objective of reducing the renal toxicity associated with cisplatin, the recommended initial dose of ETHYOL is a function of the dose of cisplatin and its administration schedule.

Dose of cisplatin	Recommended initial dose of ETHYOL	Administration schedule for ETHYOL
100-120 mg/m²	910 mg/m²	Infusion over a maximum of 15 minutes starting during the 30 minutes preceding the chemotherapy
60 mg/m² ≤ dose < 100 mg/m²	740 mg/m²	IV infusion over a maximum of 15 minutes starting during the 30 minutes preceding the chemotherapy

The blood pressure must be monitored during the infusion of ETHYOL.
The infusion of ETHYOL must be interrupted if the systolic blood pressure drops significantly from its baseline value.
If the blood pressure returns to normal within 5 minutes and if the patient is asymptomatic, the infusion can be resumed until the entire prescribed dose of ETHYOL has been administered. If it is not possible to administer the entire dose of ETHYOL, it will be necessary, during the next chemotherapy, to reduce the dose of ETHYOL by 20%.

- Radiotherapy:

When ETHYOL is to be used for the prevention of xerostomia as a complication of radiotherapy of ENT cancers, the recommended daily dose of ETHYOL is 200 mg/m^2, administered as an IV infusion over 3 minutes, starting during the 15 to 30 minutes before the session of standard fractionated radiotherapy.

The duration of treatment is dependent on the number of sessions of radiotherapy, that is to say normally 5 weekly treatments over 5 to 7 weeks.

The blood pressure must be monitored before and after the infusion."

05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicinal products

Amifostine is a prodrug that is transformed into the active substance by dephosphorylation by membrane-bound alkaline phosphatases. The differential effect in favour of healthy tissue is due to the higher activity of these phosphatases in the capillaries and at the more alkaline pH in healthy tissue. In the cells, this molecule traps free radicals and is able to detoxify alkylating agents.
ETHYOL is the only cytoprotective drug indicated in the prevention of neutropenia in ovarian cancer treated with cyclophosphamide and cisplatin, the cumulative renal toxicity of cisplatin in the treatment of advanced solid non-germinal tumours and acute and late xerostomia in ENT cancers treated by radiotherapy.

Granulocyte growth factors are indicated in the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) by means of cytotoxic chemotherapy (see Table 1).

05.2 Other health technologies

Not applicable.

◗ Conclusion

In the prevention of neutropenia in advanced ovarian carcinomas treated with cyclophosphamide and cisplatin, granulocyte growth factors are the clinically relevant comparators for ETHYOL.

In the indications in the prevention of the cumulative renal toxicity of cisplatin and in the prevention of xerostomia in ENT cancers treated by radiotherapy, there is no clinically relevant comparator for ETHYOL.

Table 1: Proprietary granulocyte growth factor products

INN	Name *Company*	Indication	Date of Opinion	AB	IAB (wording)	Reimbursed Yes/No
Filgrastim	NEUPOGEN Amgen S.A.S.	• Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception • of chronic myeloid leukaemia and myelodysplasic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and who are at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy. • Mobilisation of blood progenitor cells (BPC) in the bloodstream. • The long-term administration of filgrastrim is indicated in children and adults with severe congenital, cyclic or idiopathic neutropenia with a neutrophil count (PNN) ≤ 0.5 x 10^9/l and a history of severe or recurrent infections, in order to increase the neutrophil count and reduce the incidence and duration of infectious episodes. • Treatment of persistent neutropenia (PNN ≤ 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infection when other treatment alternatives are inadequate.	14/09/2011 (RI)	Substantial	14/12/2005 (no longer exclusively for hospital use): The administration of NEUPOGEN in patients with cancer or chronic severe neutropenia (congenital, cyclic or idiopathic) was a major therapeutic advance in the early 1990s. To this day, G-CSF growth factors, including NEUPOGEN, still play a major role in the various indications and occupy the same position in the therapeutic strategy.	Yes
	NIVESTIM Hospira France		16/02/2011	Substantial	IAB V in comparison with the proprietary medicinal product NEUPOGEN	Yes
	TEVAGRASTIM Teva Classics		04/03/2009	Substantial	IAB V in comparison with the proprietary medicinal product NEUPOGEN	Yes
	RATIOGRASTIM Ratiopharm		10/12/2008 13/01/2010	Substantial	IAB V in comparison with the proprietary medicinal product NEUPOGEN	Yes
	ZARZIO Sandoz		23/04/2014 (RI)	Substantial	24/06/2009 (inclusion): IAB V in comparison with the proprietary medicinal product NEUPOGEN	Yes

Lenograstim	GRANOCYTE Chugai Pharma France	• Reduction in the duration of neutropenia in patients (with non-myeloid • malignancy) undergoing myelosuppressive therapy followed by bone marrow transplantation and having increased risk of prolonged severe neutropenia. • Mobilisation of peripheral blood progenitor cells. • The reduction of the duration of severe neutropenia and its associated complications in patients undergoing established chemotherapy associated with a significant incidence of febrile neutropenia.	04/11/2009 (RI)	Substantial	05/05/2004 (inclusion): The administration of G-CSF growth factors, including GRANOCYTE to cancer patients was a major therapeutic advance in the early 1990s. To this day, G-CSF growth factors, including GRANOCYTE, still play a major role in the treatment of chemotherapy-induced neutropenia, and occupy the same position in the therapeutic strategy. It should be pointed out that NEULASTA, unlike GRANOCYTE, may, like NEUPOGEN, be used in children. However, GRANOCYTE, like NEUPOGEN, must be injected daily, unlike NEULASTA, which is administered as a single injection per treatment cycle.	Yes
Pegfilgrastim	NEULASTA Amgen S.A.S.	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) by means of cytotoxic chemotherapy.	07/05/2003	Substantial	NEULASTA shares with NEUPOGEN a level I IAB for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). Although no significant benefit in terms of efficacy and safety has been observed, the Committee stresses the substantial benefit in terms of ease of use and quality of life with this pegylated form of filgrastim: - a single injection per cycle of chemotherapy instead of daily administration (11 on average), reducing the demand on nursing staff - no need for repeated blood counts	Yes

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06 ANALYSIS OF AVAILABLE DATA

06.1 Efficacy

The company has provided the results of a study concerning the use of amifostine during radiotherapy that had been published in the literature.
This was a randomised, open-label, phase III study carried out by GORTEC[1] (Groupe d'Oncologie & Radiothérapie pour les cancers de la Tête & du Cou [French head & neck cancer oncology & radiotherapy group]), which compared amifostine injected by the intravenous route (in accordance with the MA; 200 mg/m^2 per day over 3 min, 15 to 30 min before irradiation) and the subcutaneous route (not in accordance with the MA; 500 mg, 2 sites, 20 to 60 min before irradiation) in 291 patients with cancer of the head and neck treated by radiotherapy.
The incidence of grade 2 or higher xerostomia (primary efficacy endpoint) was higher after use of the subcutaneous route than after use of the IV route in the 127 evaluable patients after 1 year (37% with the IV route and 62% with the SC route, p = 0.005), but not after 2 and 3 years (36% versus 51%, NS).
Applying a generalised linear mixed effects model to all the data, no significant difference between the two administration routes on the presence of grade 2 or higher xerostomia was observed.

06.2 Safety/Adverse effects

According to the SPC, the most common adverse effects observed with amifostine are nausea, vomiting and transient hypotension.
The other common adverse effects (≥ 1/100 and < 1/10) are: arrhythmia, pyrexia, rigidity, malaise, sensation of cold, hypocalcaemia, drowsiness, dizziness, syncope, rash, hypertension and hiccups.

Severe, sometimes fatal, skin reactions, including cases of erythema multiforme and rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in clinical trials and post-marketing.

Severe nonspecific allergic reactions have been reported: chills, numbness, chest pain and skin rash. Rare cases of anaphylactic-type reactions have been reported: dyspnoea, hypotension, urticaria and, rarely, cardiac arrest.

Other, rare or very rare, adverse effects have been observed post-marketing (see the SPC).

In the GORTEC sturdy, there was no difference between the IV and SC routes for amifostine in respect of patient compliance after administration of the maximum dose (69% with the IV route and 71% with the SC route). A reduction of the dose was necessary in some patients because of acute toxicity (25% versus 27%, NS) and a logistical problem (18% versus 9%, NS). Grade 1 and 2 hypotension was more common by the IV route (19% versus 8%, p = 0.01), reddening of the skin was more common by the SC route (0% versus 8%, p = 0.003). Applying a generalised linear mixed effects model to all the data, no significant difference was observed in relation to the stimulated or unstimulated rate of secretion of saliva.

[1] Bardet E, Martin L, Calais G et al. Subcutaneous compared with intravenous administration of amifostine in patients with head and neck cancer receiving radiotherapy: final results of the GORTEC 2000-02 Phase III randomized trial. J Clin Oncol 2010; 31: 1-7

07 SUMMARY AND DISCUSSION

The Committee initially considered that the benefit of this drug in the prevention of neutropenia would be limited to the prevention of neutropenia secondary to chemotherapy based on cisplatin and cyclophosphamide for stage III or IV ovarian cancer. This therapeutic contribution was judged to be moderate (level III), bearing in mind the level of efficacy of amifostine and the adverse effects linked to its use.

Two randomised open-label studies were supplied, each relating to 121 patients with stage III or IV ovarian cancer treated by 6 cycles of a combination of 1000 mg/m^2 of cyclophosphamide and 100 mg/m^2 of cisplatin with or without pretreatment with amifostine (910 mg/m^2).
The pretreatment with amifostine reduced febrile neutropenia and/or infections requiring antibiotic therapy from 21 to 8% in one study and 27% to 10% in the second compared with no pretreatment with amifostine. The protective effect was maintained throughout the cycles, and a reduction in the duration of hospitalisation and antibiotic therapy was observed.

In the extension of the indication to the prevention of the cumulative renal toxicity of cisplatin and of treatments including cisplatin, the efficacy of amifostine was evaluated in two phase III studies in 314 patients with ovarian cancer or upper aerodigestive tract cancers treated with cisplatin and cyclophosphamide. In these two studies, the protective effect was demonstrated, resulting in fewer treatment dropouts (4% among patients treated with amifostine compared with 17% in patients who were not treated with amifostine in the study relating to ovarian cancer).

No new data relating to clinical efficacy have been supplied since this first assessment of these two indications.

Within the framework of its use in radiotherapy, a randomised open-label study that included 303 patients with cancer of the head and neck who were treated by radiotherapy with or without pretreatment with amifostine was supplied. The incidence of grade 2 or higher xerostomia at 3 months and at 12 months was lower in the patients treated with amifostine: 50% versus 78% at 3 months ($p < 0.001$) and 34% versus 57% at 12 months ($p = 0.0012$).
The long-term data in 117 patients showed that the cumulative radiation dose administered before the appearance of xerostomia was higher in patients treated with amifostine (62 gray versus 42 gray, $p = 0.0001$) than in patients not treated with this drug.

The new study that was supplied, which compared the IV route of administration of amifostine with the SC route, did not permit the assessment of the value of this drug compared with the normal care strategy for patients treated by radiotherapy.

It should be stressed that none of the studies that evaluated amifostine was carried out as a double-blind study.

The adverse events most commonly observed with amifostine are hypotension and vomiting. Severe, sometimes fatal, skin reactions, including cases of erythema multiforme and rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in clinical trials and post-marketing.

08 THERAPEUTIC USE

08.1 Neutropenia due to the use of cyclophosphamide and cisplatin in patients with advanced ovarian cancer

Cytotoxic chemotherapy entails a substantial risk of haematopoietic system toxicity and can induce severe and prolonged neutropenia. This chemotherapy-induced neutropenia causes infectious complications requiring hospitalisation of the patient and may be life-threatening.
To recap, neutropenia is defined as an absolute neutrophil count (ANC) below 1.5 x 10^9/l; febrile neutropenia is defined as an ANC below 0.5 x 10^9/l with fever (axillary body temperature above 38.5°C for at least an hour) or clinical signs of sepsis.
This neutropenia is one of the major toxicities of cancer chemotherapy. It is the main cause of dose reduction or extension of the period between chemotherapy cycles, which compromises their efficacy.

The use of granulocyte growth factors (G-CSF) in oncology is recommended by ASCO[2], by ESMO[3] and the European Organisation for Research and Treatment of Cancer EORTC[4].
They may be prescribed, in special cases, for primary prevention if the risk of febrile neutropenia is ≥ *20%* or even 10% in some patients in whom the risk factors justify it (particularly age > 65 years, advanced stage of the disease, one or more prior episodes of febrile neutropenia, no antibiotic or G-CSF therapy, impaired nutritional status, cytopenia related to invasive spinal tumour, and extensive prior treatment(s), including wide area irradiation or combination chemotherapy). They may also be used in secondary prevention if the intensity of chemotherapy cannot be reduced and in curative treatment in the event of serious signs such as established disorder or risk of sepsis (systemic fungal infection, septic syndrome etc.).

ASCO recommended in 2008 that the use of amifostine could be considered, but taking into consideration other possible strategies, which is to say, the administration of granulocyte growth factors and reduction of the dose of chemotherapy. However, this recommendation is based on a collection of studies with a low level of evidence (open-label studies without placebo comparison, small numbers of patients) that have produced contradictory results (2 positive studies in ovarian cancer out of 11).

Current therapeutic use
Currently, amifostine no longer has a role in the prevention of neutropenia secondary to chemotherapy based on cisplatin and cyclophosphamide for advanced ovarian cancer because its efficacy is based on a low level of evidence, its safety is poor (hypotension requiring close monitoring of the patient in a hospital environment, risk of serious adverse skin reactions such as *Stevens-Johnson syndrome or* toxic epidermal necrolysis, which are potentially life-threatening for the patient) and because this combined chemotherapy is no longer used in ovarian cancer.

[2] American Society of Clinical Oncology Practice:
Smith Thomas J. and al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An
Evidence-Based Clinical Practice Guideline. ASCO 2006; 24, number 19
[3] European Society for Medical Oncology:
Crawford J et al. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol
2010; 21(supplement 5): v248-v251
[4] European Organisation for Research and Treatment of Cancer:
Landré T. Recommandation EORTC sur l'utilisation des GCS-F dans la prévention des neutropénies fébriles chimio-induites. onKo 2013; 5: 27-29

08.2 Cumulative renal toxicity of cisplatin and of treatments including cisplatin in advanced solid non-germinal tumours

Cisplatin can trigger acute anuric renal failure resulting from tubulopathy (necrosis of the distal convoluted tubules and collecting tubules) during the 24 hours after its administration at doses > 50 mg/m^2. This is partially reversible over 3 weeks, with an induction phase of 48 hours with polyuria, then a plateau phase of 2 to 7 days, followed by a remission phase of 3 weeks. Cumulative doses of cisplatin > 700 mg/m^2 can induce chronic renal failure. Hypomagnesaemia and hypocalcaemia are the early laboratory signs.

Preventive treatment comprises correction of existing electrolyte anomalies, institution of hyperhydration including the administration of cisplatin together with magnesium and calcium, and limitation of the infusion rate[5]. Cisplatin must not be combined with other nephrotoxic or diuretic drugs.
There is no recommendation regarding the use of amifostine in the prevention of cumulative renal toxicity due to cisplatin.

Current position of amifostine
Due to the poor quality of the demonstration of its efficacy and its poor safety, with, in particular, a risk of hypotension, requiring close monitoring of the patient in a hospital environment, risk of serious adverse skin reactions (such as Stevens-Johnson syndrome or toxic epidermal necrolysis), which are potentially life threatening for the patient, amifostine no longer has a place in the therapeutic strategy.

08.3 Prevention of acute and late xerostomia in ENT cancers, in combination with standard fractionated radiotherapy."

According to the American guidelines of the NCCN[6] (2008) and ASCO[7] (2008), the prevention of mucositis during the treatment of cancer requires good oral hygiene as well as a dental examination and any necessary dental treatment, to avoid sources of infection and regions at risk of exacerbating xerostomia. It is recommended that dietary habits should be changed to avoid foodstuffs that could injure the buccal mucosa as a result of their coarse texture or excessive chewing.
The NCCN recommends the use of devices that permit positioning of the tongue and protection of the soft tissue from secondary radiation due to the presence of metallic components in the teeth.
Amifostine has been recommended for the prevention of xerostomia due to standard fractionated radiotherapy of the head and neck, but this recommendation does not constitute a consensus because of the methodological weaknesses of the studies (small groups of patients, single-centre studies, open-label studies, no comparison with placebo, inclusion of patients at an advanced stage treated by a combination of radiotherapy and chemotherapy) and the contradictory results, as emphasised by the MASCC[8]. Moreover, disagreement about the use of amifostine is due to its adverse effects and to the fact that the risk of mucositis may be reduced by the use of conformal radiotherapy with modulation of the intensity.

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[5] Launat-Vacher V et al. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. Cancer Chemother Pharmacol. 2008; 61: 903-9

[6] National Comprehensive Cancer Network: Bensinger W et al. NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care. Journal of the National Comprehensive Cancer Network 2008; 6: S1-24

[7] American Society of Clinical Oncology: Hensley ML and al. American Society of Clinical Oncology 2008 Clinical practice Guideline update: Use of chemotherapy and radiation therapy protectants.J Clin Oncol 2009: 27: 127-45

[8] Multinational Association of Supportive Cancer Care:
Keefe DM et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007; 109: 820-31

The guidelines of the GPIC and the AFSOS (2011)[9] also stress the importance of oral hygiene before radiotherapy, dietary measures and protective devices (lead dental protectors). There is no mention of amifostine in these guidelines.

Current position of amifostine
Due to the poor quality of the demonstration of its efficacy within the framework of standard fractionated radiotherapy, its poor safety, with, in particular, a risk of hypotension, requiring close monitoring of the patient in a hospital environment, risk of serious adverse skin reactions (such as Stevens-Johnson syndrome or toxic epidermal necrolysis), which are potentially life threatening for the patient, and the development of conformal radiotherapy with modulation of the intensity, which permits the selective irradiation of specific tissues, amifostine no longer has a role in the prevention of acute or late xerostomia in ENT tumours treated by radiotherapy.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

09.1 Actual benefit

9.1.1 Prevention of neutropenia due to the use of cyclophosphamide and cisplatin in patients with advanced ovarian cancer

◗ Neutropenia is a common complication of chemotherapy. If may lead to infectious complications that may be life-threatening.

◗ This proprietary medicinal product is intended as preventive therapy.

◗ The demonstration of the efficacy of amifostine is based on studies with a low level of evidence. Amifostine is poorly tolerated, with a risk of cardiovascular disorders (in particular hypotension) requiring close monitoring of the patient in a hospital environment, and rare but serious skin toxicity that is potentially life threatening for the patient (Stevens-Johnson syndrome or toxic epidermal necrolysis). The efficacy/adverse effects ratio is low.

◗ Amifostine no longer has a role in the prevention of neutropenia secondary to chemotherapy based on cisplatin and cyclophosphamide for advanced ovarian cancer in view of the low level of evidence of the demonstration of its efficacy, its poor safety, and the abandonment of this combined chemotherapy in this indication.

◗ There are no treatment alternatives in the same pharmacotherapeutic category. Granulocyte growth factors can be used in the treatment and prevention of neutropenia following chemotherapy.

Consequently, the Committee considers that the actual benefit of ETHYOL in the prevention of the risk of neutropenia and its consequences (in particular infections) due to the combined use of cyclophosphamide and cisplatin in patients with advanced ovarian cancer (FIGO stage III or IV) is insufficient for reimbursement by National Health Insurance.

[9] Groupe pour la prévention des infections en cancérologie et Association francophone pour les soins oncologiques de support: Prévention et traitement des mucites buccales chimio et/ou radio induites. http://www.afsos.org/IMG/pdf/procedure_mucite_gpic-afsos_V3.pdf

9.1.2 Prevention of the cumulative renal toxicity of cisplatin and of treatments including cisplatin in advanced solid non-germinal tumours

◗ Cisplatin can trigger acute renal failure, generally partially reversible after 3 weeks, at cumulative doses between 50 and 120 mg/m^2.

◗ This proprietary medicinal product is intended as preventive therapy.

◗ The demonstration of the efficacy of amifostine is based on studies with a low level of evidence. Amifostine is poorly tolerated, with a risk of cardiovascular disorders (in particular hypotension requiring close monitoring of the patient in a hospital environment), and rare but serious skin toxicity that is potentially life threatening for the patient (Stevens-Johnson syndrome or toxic epidermal necrolysis). The efficacy/adverse effects ratio is low.

◗ Due to the poor quality of the demonstration of its efficacy and its poor safety, amifostine no longer has a role in the prevention of renal toxicity linked to cisplatin.

◗ There is no alternative drug treatment. The prevention of renal toxicity linked to cisplatin is based on prior correction of electrolyte levels, supplementation of calcium and magnesium, limitation of the speed of the infusion of cisplatin, and avoiding any combination with other nephrotoxic drugs.

Consequently, the Committee considers that the actual benefit of ETHYOL in the prevention of the cumulative renal toxicity of cisplatin and of treatments including cisplatin when the unit doses thereof are between 60 and 120 mg/m^2, in combination with measures to ensure adequate hydration in patients with advanced solid non-germinal tumours, is insufficient for reimbursement by National Health Insurance.

9.1.3 Prevention of acute and late xerostomia in ENT cancers, in combination with standard fractionated radiotherapy

◗ Acute or late xerostomia is an extremely common (4 patients out of 5) side effect of the treatment of ENT cancers by radiotherapy. Its occurrence may compromise the continuation of treatment and its consequences (digestive, phonation, necrosis of the jaw) leading to a marked deterioration in the quality of life.

◗ This proprietary medicinal product is intended as preventive therapy.

◗ The demonstration of the efficacy of amifostine is based on studies with a low level of evidence. Amifostine is poorly tolerated, with a risk of cardiovascular disorders (in particular hypotension requiring close monitoring of the patient in a hospital environment), and rare but serious skin toxicity that is potentially life threatening for the patient (Stevens-Johnson syndrome or toxic epidermal necrolysis). The efficacy/adverse effects ratio is low.

◗ Due to the poor quality of the demonstration of its efficacy within the framework of fractionated radiotherapy, its poor safety, and the development of conformal radiotherapy with modulation of the intensity, which permits the selective irradiation of specific tissues, amifostine no longer has a role in the prevention of acute or late xerostomia in ENT tumours treated by radiotherapy.

◗ There is no alternative drug treatment. The prevention of acute and late xerostomia in the treatment of ENT cancers by radiotherapy is based on hygiene and dietary measures, prior dental treatment, the use of protective devices, and the use of conformal radiotherapy with modulation of the intensity.

Consequently, the Committee considers that the actual benefit of ETHYOL in the prevention of acute and late xerostomia in combination with standard fractionated radiotherapy in ENT cancers is insufficient for reimbursement by National Health Insurance.

09.2 Improvement in actual benefit (IAB)

As the actual benefit is insufficient, an assessment of the improvement in actual benefit brought about by ETHYOL is not appropriate.