HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

09 July 2014

PHOTOFRIN 75 mg, powder for solution for injection

B/1 type 1 glass vial (CIP: 34009 559 492 6 8)

Applicant: BIOPROJET

INN	porfimer sodium
ATC code (2014)	L01XD01 (sensitizers used in photodynamic therapy)
Reason for the review	**Reassessment of the IAB following joint referral from the Ministry of Health, the Social Security Directorate and the Directorate-General for Health Services on 10 October 2013, in accordance with article R 163-19 of the Social Security Code.**
Lists concerned	**Hospital use (Public Health Code L.5123-2)**
Indications concerned	**“Treatment of recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment.”**

Actual Benefit	**Low.**
Improvement in Actual Benefit	**Based on the current data, PHOTOFRIN does not provide any improvement in actual benefit (level V, non-existent) compared with the currently available therapies in the treatment of recurrent non-small cell lung cancer or oesophageal cancer.**
Therapeutic use	**Due to the small number of patients likely to benefit from palliative photodynamic therapy with PHOTOFRIN, and according to expert opinion, this medicine has a very limited role in the therapeutic strategy for recurrent non-small cell lung cancer or oesophageal cancer.**
Target population	**The target population for PHOTOFRIN can be estimated as 20 patients/year.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	09 April 1996 (national procedure)
Prescribing and dispensing conditions / special status	List I Medicinal product for hospital use only

ATC Classification	2014	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XD	Sensitizers used in photodynamic/radiation therapy
	L01XD01	porfimer sodium

02 BACKGROUND

As part of the Hospitalisation Council's work updating the list of medicinal products that are chargeable in addition to hospital services, and pursuant to article R 163-19 of the 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 PHOTOFRIN 75 mg, concentrate for solution for infusion, the subject of this opinion.

Porfimer sodium, the active substance in PHOTOFRIN, is a photosensitising agent used in photodynamic therapy (PDT).
Photodynamic therapy (PDT) involves exposing tumour cells to a laser light after they have been photosensitised by administering a pharmacological agent systemically or locally.
This light-sensitive medicine (photosensitizer) is injected intravenously. It is taken up and accumulated primarily by malignant tumours, but remains inactive until it is exposed to a laser light of the correct wavelength. When it absorbs light, porfimer sodium acquires energy and changes from an inactive state to an excited state. Excited porfimer has excess energy which is rapidly dispersed through an intermediate "triplet" state that is responsible for the photosensitisation phenomena; excess energy from the triplet state may be transferred to oxygen, which then becomes excited and is known as singlet oxygen. As well as singlet oxygen, free radicals (superoxide and hydroxyl) are also formed. Although the complete mechanism is not fully known, the singlet oxygen and free radicals seem to be the main cytotoxic agents.

03 THERAPEUTIC INDICATIONS

"Treatment of recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment."

04 DOSAGE

"Dosage:
2 mg/kg administered as a single slow intravenous injection over 3 to 5 minutes.

Photoactivation of PHOTOFRIN:
PHOTOFRIN is activated by light in the spectral region of 630 nm. Approximately 40-50 hours after PHOTOFRIN administration, laser light should be delivered to the tumour by a cylindrical fibre optic diffuser or a microlens fibre optic passed through the operating channel of an endoscope/bronchoscope.

Monitoring:
Endobronchial tumours associated with non-small cell lung cancer:
Patients should be monitored closely after laser irradiation; if dyspnoea or haemoptysis occurs or worsens, emergency bronchoscopy and debridement may be required.
If there are no complications, two days after irradiation, the patient should undergo bronchoscopic debridement to remove the necrotic tissue.
If there is residual tumour after bronchoscopic debridement, laser irradiation may be repeated with the same characteristics as the first treatment; a second injection of PHOTOFRIN is not necessary in this particular case. This second laser irradiation should be administered 96 to 120 hours after the initial PHOTOFRIN injection. A second bronchoscopic debridement should be performed 2 days after irradiation, or earlier if necessary.

Oesophageal cancer:
If residual tumour is visible on endoscopy after photodynamic therapy, laser irradiation may be repeated with the same characteristics as the first irradiation; a second injection of PHOTOFRIN is not necessary in this particular case. This second laser irradiation should be administered 96 to 120 hours after the initial PHOTOFRIN injection."

05 THERAPEUTIC NEED

05.1 Oesophageal cancer

Most oesophageal cancers are diagnosed at an advanced stage (poor prognosis). The seriousness of the cancer mainly relates to how far it has spread at the time of diagnosis. The majority of patients are therefore managed in the palliative stage with the aim of treating dysphagia. Dysphagia in advanced oesophageal cancer affects patients' nutritional status and quality of life. In this case, the objective of treatment is to maintain oral feeding.
The national guidelines[1] on managing oesophageal cancer were produced jointly by HAS, the National Cancer Institute (INCa) and several learned societies in 2011. They describe the different

[1] LTC guide no. 30, "Cancer de l'œsophage" [Oesophageal Cancer] by the Haute Autorité de Santé and INCa – September 2011. Available online: [URL]: http://www.has-sante.fr/portail/jcms/c_1105133/fr/ald-n-30-cancer-de-l-oesophage

therapeutic strategies based on histological type (squamous cell carcinoma/adenocarcinoma) and cancer stage:

- For early forms (high-grade dysplasia and intramucosal carcinoma):

- Standard treatment: endoscopic mucosal resection.

- For localised stages:

- Standard treatment: surgery alone;
- Chemotherapy followed by surgery may be considered in cases of localised cancer where lymph node involvement is suspected.

- For locally advanced stages:

- There is growing evidence that preoperative chemoradiotherapy is useful in adenocarcinoma;
- Chemoradiotherapy followed by surgery may be considered in cases of locally advanced squamous cell carcinoma, particularly if there is residual tumour after chemoradiotherapy;
- Chemoradiotherapy alone may be provided as curative treatment for locally advanced squamous cell carcinoma, or for any histological type if surgery is contraindicated;
- Chemotherapy followed by surgery may be considered in cases of locally advanced adenocarcinoma of the lower third which seems easy to resect;
- Purely symptomatic treatment (endoprosthesis, etc.) may also be offered if the patient so desires.

- For metastatic stages:

- Palliative chemotherapy is the most common treatment. Purely symptomatic treatment (endoprosthesis, etc.) may also be offered.

Symptomatic treatment mainly involves managing:

- Pain;
- Toxicity from chemotherapy and/or radiotherapy;
- Psychological changes;
- **Dysphagia and its effect on nutritional status:**

➢ **<u>If the patient is operable or having curative treatment, re-feeding methods include:</u>**

- As 1st-line therapy, oral supplements or enteral tube feeding;
- As 2nd-line therapy, a jejunostomy;
- As 3rd-line therapy, parenteral nutrition.

➢ **<u>If the patient is not having curative treatment, the methods of removing obstruction are:</u>**

- **Placement of an oesophageal endoprosthesis;**
- **High dose rate curietherapy;**
- **External radiotherapy with appropriate dose fractionation.**

The therapeutic need is therefore partially met by a range of therapeutic techniques. The possibility of using photodynamic therapy is not described in these guidelines.
Until recently, PHOTOFRIN was the only photosensitizer approved in both the USA and Europe. It is used in palliative care for patients with a tumour blocking the oesophagus. The prolonged period of photosensitivity following its use (6 weeks) is an adverse effect that affects patients' quality of life. This has led to the development of second-generation photosensitizers. They include 5-aminolevulinic acid (LEVULAN), used in actinic keratosis, basal cell carcinoma since it acts at a depth of 1.5 mm (photosensitivity = 1 to 2 days), and dysplastic lesions in Barrett's oesophagus; and verteporfin (VISUDYNE) or mTHPC (FOSCAN), used as palliative treatment for head and neck cancers (photosensitivity = 2 to 4 weeks).
Finally, third-generation photosensitizers are being developed. These will require activation by a long wavelength, leading to a shorter period of photosensitivity and better tumour specificity.

05.2 Non-small cell lung cancer

The national guidelines[2] for managing non-small cell lung cancer were produced in 2010 by INCa and describe the different therapeutic strategies based on the stage of the disease.

Symptom management (pain, nutrition, etc.) is an integral part of these patients' care.

- **Chest symptoms**

If chest symptoms (cough, haemoptysis, chest pain and dyspnoea) are predominantly severe, palliative thoracic radiotherapy may be offered, depending on the aetiology of the symptoms.

- **Bronchial obstruction**

- Serious proximal endobronchial obstructions (of the trachea and/or main bronchi, sometimes the lobar bronchi) should be cleared using radiotherapy, laser resection, thermocoagulation or cryotherapy. This should be done by a trained operator who will judge whether it is appropriate to complete the procedure by fitting an endoluminal prosthesis, particularly in the case of major extrinsic compression of the bronchial lumen.
- If a bronchial obstruction recurs after a previous radiotherapy treatment, curietherapy may be considered.

- **Cerebral metastases**

Cerebral hypofractionated radiotherapy is the standard treatment for symptoms associated with multiple cerebral metastases (> 3).

- **Symptomatic pleural effusion**

- In cases of recurrent free neoplastic pleural effusion in an untrapped lung, the standard treatment is thoracoscopic talc pleurodesis.
- If thoracoscopic talc pleurodesis cannot be performed, intrapleural instillation of a talc suspension may be considered. Percutaneous drainage with an indwelling catheter is reserved for exceptional situations.

The therapeutic need is therefore partially met by a range of therapeutic techniques. The possibility of using photodynamic therapy to remove obstructions in the bronchi is not described in these guidelines.

[2] Recommandations professionnelles. Cancer du poumon non à petites cellules [Professional guidelines. Non-small cell lung cancer]. Collection Recommandations & référentiels, INCa, Boulogne-Billancourt, September 2010. Available online: [URL]: http://www.e-cancer.fr/publications/55-recommandations-de-pratique-clinique/603-prise-en-charge-therapeutique-du-cancer-du-poumon-non-a-petites-cellules-synthese-des-recommandations

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Although there are medicinal products that aim to make cancer cells photosensitive (METVIXIA, EFFALA, FOSCAN), none are indicated in oesophageal cancer or non-small cell lung cancer.

06.2 Other health technologies

In the palliative treatment of recurrent obstructive oesophageal cancer, the placement of a prosthesis (expansive or non-expansive), with or without prior endoscopic resection, is the standard technique.

To remove endobronchial obstructions, radiotherapy, laser resection, thermocoagulation or cryotherapy are the standard techniques with curietherapy as a second-line treatment.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

PHOTOFRIN has Marketing Authorisation in Argentina, Canada, the USA, Europe, Mexico and Japan but its indications vary by country.

Country	Reimbursed	
	Yes (give start date) / No / Under assessment or duly documented change	Scope (indications) and special condition(s)
Germany, United Kingdom	Yes	Same indication as French MA

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for the request)	22 April 1998 (application for inclusion for hospital use)
Indication	"Treatment of recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment."
Actual Benefit (wording)	"Non-small cell lung cancer and oesophageal cancer are serious conditions. Porfimer sodium has been shown to be effective in recurrences of these indications. The alternatives are not drug treatments. Bronchial obstructions may be removed using laser therapy and oesophageal obstructions using techniques such as endoprostheses or intracavitary curietherapy. The role of light therapy in the therapeutic strategy for recurrent non-small cell lung cancer or oesophageal cancer is relatively minor." N.B.: The level of actual benefit was not defined at the time of the vote for the previous Transparency Committee opinion; actual benefit corresponded to a set of criteria only.
Improvement in Actual Benefit (wording)	PHOTOFRIN 75 mg, lyophilisate for parenteral use provides a moderate (level III) improvement in actual benefit, in terms of symptomatic efficacy compared with the currently available therapies for the treatment of recurrent non-small cell lung cancer or oesophageal cancer.
Therapeutic use	The role of light therapy in the therapeutic strategy for recurrent non-small cell lung cancer or oesophageal cancer is relatively minor.

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

No new studies have been submitted by the company. The efficacy data come from the literature. In the studies and reviews described below, photodynamic therapy (PDT) is given using porfimer sodium. Note that this is the only photosensitizer that has this indication and is activated by a well-defined wavelength.

Two cohort studies and one prospective randomised study evaluated the efficacy of photodynamic therapy as palliative treatment for dysphagia in advanced oesophageal cancer.

Litle et al. study:[3] A retrospective study aiming to evaluate the efficacy of photodynamic therapy (PDT) in terms of improvement in dysphagia scores, duration of reduction of dysphagia, occurrence of complications and overall survival. This study included 215 patients treated with 318 courses of PDT between 1996 and 2002 (165 men/50 women, average age = 69.0 years). Of these patients, 129 (60%) had not received any previous treatment, 27 (13%) had previously been treated with chemotherapy, 19 (9%) with chemoradiotherapy, 7 (3%) with radiotherapy, 16 (7%) with an oesophagectomy and 29 (14%) with stent placement.
295 of the 318 PDT courses were administered for oesophageal obstruction, 15 for bleeding and 8 for other reasons.
The stage of dysphagia was determined using a scale from 1 (asymptomatic) to 5 (impossible to swallow anything, including saliva) just before the PDT course and 2 to 4 weeks after it. These scores were obtained for 251 courses (the number of patients is not specified by the authors).
An improvement in dysphagia score by at least 1 point was observed in 85% of patients, with a mean score reduction from 3 to 2 (90% CI = [0; -2], $p<0.0001$).
For the 95 patients who received two courses of PDT, the mean duration of reduction in malignant dysphagia was 66 days before a new course of PDT was needed. The procedure-related mortality rate was 1.8%. The median overall survival after the first course of PDT was 4.8 months.
In terms of safety, the following adverse events were described: 19 cases of photosensitivity, 11 of pleural effusion, 5 of oesophageal perforation and 5 of stricture of the oesophageal lumen.
According to the authors, PDT should be preferred when treating large tumours as it causes less thermal damage to tissue than other laser therapies.

Yoon et al. study:[4] A prospective, non-comparative, non-randomised study aiming to evaluate the efficacy of photodynamic therapy (PDT) in a multimodal approach for palliative treatment of dysphagia in advanced oesophageal cancer. A total of 20 patients were included between 2001 and 2003 (18 men and 2 women, with an average age of 66 years). The primary efficacy endpoint was the impact of treatment on dysphagia. The stage of dysphagia was determined using a scale from 1 (difficulty swallowing solid foods) to 4 (impossible to swallow anything, including saliva). The dysphagia was considered to have improved if the dysphagia score fell by at least one point between the day of treatment and the patient's follow-up 4 weeks after the PDT session.
A total of 5 patients were treated with PDT only and 15 were treated with PDT combined with radiotherapy or with the placement of an oesophageal stent.
At 4 weeks post-PDT, an improvement in dysphagia score was observed in 18/20 patients, with a reduction in mean score from 2.75 ± 0.91 to 1.05 ± 0.83 ($p<0.05$).

Several statistical and methodological weaknesses must be emphasised:

[3] Litle VR, Luketich JD, Christie NA, Buenaventura PO, Alvelo-Rivera M, McCaughan JS et al. Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. Ann Thorac Surg 2003;76:1687-92
[4] Yoon HY, Cheon YK, Choi HJ, Shim CS. Role of photodynamic therapy in the palliation of obstructing esophageal cancer. Korean J Intern Med 2012;27:278-84

- The potential biases associated with a non-comparative design, particularly selection bias, follow-up bias and measurement bias.
- The number of patients included is very low.

On the whole, taking these points into account, the level of evidence for the results of these 2 studies is low. Therefore, these results can only be considered exploratory and they cannot be used to precisely and reliably quantify the effect of treatment.

Rupinski et al. study:[5] A randomised study aiming to evaluate which of 3 palliative treatment regimens for advanced oesophageal cancer obtain the longest dysphagia-free period. A total of 93 patients were randomised. The analysis was performed in the per-protocol population (patients with tracheal and/or bronchial infiltration were excluded).

The three treatment arms were:

- Argon plasma coagulation alone (control arm) (n=27 patients)
- Argon plasma coagulation + brachytherapy (HDR) (n=27 patients)
- Argon plasma coagulation + photodynamic therapy (PDT) (n=26 patients)

Twenty two patients per group were required in order to observe a statistically significant difference between two treatment arms, for dysphagia-free periods of between 35 and 95 days in each arm, with a two-tailed alpha risk of 0.05 and a power of 80%. To maintain that power over three arms, the sample size had to be multiplied by 1.23, and thus a minimum of 27 patients were needed in each of the three arms. The log-rank test was used with data censored from the day of dysphagia recurrence in treated patients.

Note that the log-rank test is a standard test for comparing two curves (often survival curves). When it is significant, the hypothesis that the two curves are superimposable can be rejected. It analyses whether, overall, at the level of each occurrence of an event (death, a particular symptom, etc.), the distance between the two curves is greater than could be explained by chance. It is not used to quantify a difference but to determine whether a statistically significant difference exists between two curves. Consequently, the statistical analysis plan did not have to quantify an expected difference in its hypothesis.

The dysphagia-free period was greater in the two arms combining two different techniques than in the control arm (HDR vs control, p = 0.002 and PDT vs control, p = 0.036). The mean duration was 88 days in the argon plasma coagulation + brachytherapy arm, 59 days in the argon plasma coagulation + PDT arm and 35 days in the control arm.

In terms of safety, it should be noted that fever occurred in 3 patients and that dysphagia worsened in 6 patients in the PDT arm.

The conclusions of this study suggest incorporating PDT into a multimodal approach for managing this type of patient.

The number of patients included in this study is low, since the log-rank test remains a very conservative test, which is one of its limitations. In addition, the number of patients required in the statistical analysis plan was not achieved in one of the treatment arms.

A literature review evaluated and discussed the role of photodynamic therapy in the therapeutic management of non-small cell lung cancer and advanced oesophageal cancer.

The literature review[6] was undertaken by the Centre for Reviews and Dissemination at the University of York as part of the HTA, a British programme aiming to provide quality data to NHS decision-makers.

[5] Rupinski M, Zagorowicz E, Regula J, Fijuth J, Kraszewska E, Polkowski M et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). Am J Gastroenterol 2011;106:1612-20

[6] Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. Centre for Reviews and Dissemination (CRD), University of York, York, UK. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess 2010;14:1-288

The objective was to carry out a review of the efficacy and safety data for photodynamic therapy (PDT) when used in various malignant diseases.
A total of 88 trials reported in 141 publications were included. Among these, 7 trials covered the use of PDT to treat non-small cell lung cancer (NSCLC) and 13 trials covered its use to treat oesophageal cancer.

- In the treatment of NSCLC, the authors report that PDT is used only as palliative therapy and that further research is needed to determine its role and position versus the current comparator treatments. Finally, certain subgroups of the population (the authors do not specify which subgroups) seem to benefit more from this therapy.
- In the treatment of oesophageal cancer, the authors report that clinical trials have been conducted in both curative and palliative therapy, but that no conclusions can be drawn as to the role of PDT, which is yet to be defined. Comparative studies versus relevant comparators (the authors do not specify which comparators) are needed to determine the efficacy of PDT, its impact on patients' quality of life and its safety profile.

09.2 Adverse effects

◗ The company has provided new safety data (PSURs covering the period 20/04/2012 to 19/04/2013).
These data do not change the safety profile of this proprietary medicinal product. Nonetheless, in Japan 4 articles report 46 cases of oesophageal stenosis occurring in patients treated with PHOTOFRIN. The SPC was not amended and the competent authorities have not made any requests to the company.

◗ SPC data

The only systemic effects expected with PHOTOFRIN are transient photosensitivity lasting 4 to 6 weeks and moderate constipation.
Photosensitivity reactions
Photosensitivity reactions occurred in approximately 20% of patients treated with PHOTOFRIN in clinical trials. These reactions were mostly mild to moderate erythema but they also included swelling, itching, burning sensation, feeling hot or blisters.

Other adverse effects vary depending on the indication:
Oesophageal cancer
The inflammatory reaction triggered by the photodynamic effect may manifest as oesophageal oedema, pain, pleural effusion and fever and may lead to atrial fibrillation.
• Adverse effects occurring in more than 10% of cases are: abdominal pain, nausea, vomiting, dyspnoea, pneumonia, chest pain, respiratory failure, haematemesis and anaemia, fever.
• Adverse effects occurring in fewer than 10% of cases are: diarrhoea, dehydration, atrial fibrillation, generalised or localised oedema, infection, oesophageal fistula, dysphagia, weight loss.

Lung cancer
Transient worsening of pulmonary symptoms such as dyspnoea or haemoptysis may be seen after photodynamic therapy with PHOTOFRIN. This is caused by local oedema, increased bronchial secretion or mucositis.
Patients should be monitored carefully between administration of the laser irradiation and the planned bronchoscopic debridement for removing necrotic tumour debris.
Worsening of pulmonary signs may require immediate endoscopic ablation of tumour debris or mucous secretions.
Severe haemoptysis or pulmonary haemorrhage, associated with erosion of the bronchial or pulmonary arteries or with the treatment of tumours near these blood vessels, may occur during bronchoscopic debridement or spontaneously within a few weeks of treatment.
Adverse effects observed in more than 10% of cases are: transient worsening of dyspnoea, cough, haemoptysis, bronchitis, pneumonia, fever.

Adverse effects observed in fewer than 10% of cases are: increased bronchial secretion, nausea, respiratory failure, vomiting.
Many adverse effects are commonly caused by the disease treated or by bronchoscopy with transbronchial biopsy.
Cases of a transient increase in vascular permeability with hypovolaemia or peripheral or generalised oedema occurring 1 to 5 days after light therapy with PHOTOFRIN have also been reported, most commonly in patients with disseminated intraperitoneal tumours.

◗ Data from the literature

One study evaluated and discussed pharmacokinetic and safety data for porfimer sodium. This was **Pereira et al.,**[7] an open-label, single-arm study that aimed to evaluate pharmacokinetic data together with safety data for porfimer sodium after an initial dose then a second dose (administered 30 to 45 days after the first dose) in patients treated with photodynamic therapy (PDT).
This study included 19 patients with an average age of 66 years. Blood samples were taken before each injection, then post-dose at 5 minutes, 1, 12, 24, 48 and 72 hours, and 5, 8, 15, 22, 29 and 36 days (if no second injection was given between 30 and 36 days).
The mean elimination half-life after the first injection was 410 hours, i.e. 17 days (n=19 patients). This increased to a mean of 725 hours after the second injection (n=14 patients). Porfimer sodium therefore seems to accumulate as injections are administered, which can be explained by its particularly long half-life. It is thus not completely eliminated (note that a product is considered to be eliminated after 3.32 half-lives) at the time of the second injection. No difference in C_{max} was observed between the two injections.

The safety profile was the same after the first and second injections.
Nine serious adverse events occurred in 8 patients (4 deaths including 3 related to disease progression and 1 following cardiac arrest, 1 case of dehydration and 1 case of cholangitis). Photosensitivity was the only serious adverse event considered to be treatment-related. Finally, 8 patients described 9 treatment-related adverse events (including 5 cases of photosensitivity); these events were all classed as skin and subcutaneous tissue disorders.
Repeated administration of porfimer sodium does not seem to affect the safety of the product.

In conclusion, the level of evidence of these results is low due to the small number of patients included and the methodology of this study (open-label). Therefore, these results can only be considered exploratory.

09.3 Usage/prescription data

According to GERS data from March 2013 to February 2014, the hospital sales in common dispensing units were 54 units i.e. 54 vials.

09.4 Summary & discussion

PHOTOFRIN is used in advanced oesophageal cancers with the aim of removing obstructions and enlarging the oesophageal lumen. In this case, it is administered as palliative treatment, with its main benefit being relief of dysphagia.

The aim of using PHOTOFRIN in obstructive lung cancers is to relieve symptoms, in cases where the tumour has recurred following surgical resection or radiotherapy.

[7] Pereira SP, Ayaru L, Ackroyd R, Mitton D, Fullarton G, Zammit M et al. The pharmacokinetics and safety of porfimer after repeated administration 30-45 days apart to patients undergoing photodynamic therapy. Aliment Pharmacol Ther 2010;32:821-7

Photodynamic therapy (PDT):

- can have a selective and targeted action. The area of necrosis generally does not exceed 10 mm and neighbouring healthy tissue is spared;
- requires only one administration of photosensitizer, unlike chemotherapy and radiotherapy which require several courses;
- may be repeated several times (usually every 8 weeks) and on the same treatment area if necessary.

However, no conclusions can be drawn from the studies published in the literature as to the efficacy of PHOTOFRIN and photodynamic therapy in advanced oesophageal cancer or non-small cell lung cancer. There are no data on quality of life relating to the use of this medicine. There are no data versus oesophageal radiofrequency ablation.

The safety profile for this proprietary medicinal product is characterised by a prolonged period of photosensitivity (4 to 6 weeks) following use, an adverse effect that can affect patients' quality of life.

Serious adverse effects have been observed during the use of PDT with PHOTOFRIN: transient worsening of dyspnoea, severe haemoptysis or pulmonary haemorrhage, respiratory failure, atrial fibrillation, generalised or localised oedema, haematemesis, perforation (although it is not possible to differentiate between the direct role of the procedure or other factors such as previous or concomitant treatments, and tumour progression).

09.5 Planned studies

An application for Marketing Authorisation is under assessment, for the use of PHOTOFRIN to treat advanced, non-resectable hilar cholangiocarcinoma with cholestasis in combination with retrievable stents.

010 THERAPEUTIC USE

The role of PHOTOFRIN and photodynamic therapy in the treatment of recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment is not mentioned in international guidelines.**Erreur ! Signet non défini.**[8,9,10]

Guidelines by the Upper Gastrointestinal Surgeons of Great Britain, the British Society of Gastroenterology and the British Association of Surgical Oncology**Erreur ! Signet non défini.** view photodynamic therapy as experimental and do not recommend it among the palliative treatments for oesophageal cancer.
For several years, the preferred indication for photodynamic therapy seemed to be the treatment of superficial forms of cancer and high-grade dysplasia in Barrett's oesophagus (off-label use), but this technique appears to have been supplanted by mucosal resection and radiofrequency ablation and it remains under evaluation in France.
According to expert opinion, this medicinal product may be used with the aim of reducing dysphagia to allow sufficient intake of calories and avoid artificial feeding via a tube or gastrostomy.

The use of photodynamic therapy in the treatment of recurrent non-small cell lung cancer is not discussed in international guidelines.
According to expert opinion, the use of this medicine in this indication may be considered obsolete; emergency removal of bronchial obstruction is necessary in the vast majority of cases, and it is impossible to use the product under these circumstances. By contrast, the current most common use of the product is off-label use, namely the treatment of carcinoma in situ (CIS), which by definition cannot be detected radiologically. This requires endobronchial treatment, for which it is crucial that lesions are defined precisely through a comprehensive assessment (they are most often multifocal). Consequently, the current use of the product in lung cancer strays quite far from its indications.

Due to the small number of patients likely to benefit from palliative photodynamic therapy with PHOTOFRIN, and according to expert opinion, this medicine has a very limited role in the therapeutic strategy for recurrent non-small cell lung cancer or oesophageal cancer.

[8] Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D, on behalf of the ESMO guidelines working group. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi51-6.
[9] Vansteenkiste J, De Ruysscher D, Eberhardt W.E.E, Lim E, Senan S, Felip E et al. on behalf of the ESMO Guidelines of the ESMO guidelines working group. Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi89-98.
[10] Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. on behalf of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. Gut 2011;60:1449-72.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- Non-small cell lung cancer and oesophageal cancer are life-threatening diseases.
- This is a palliative treatment.
- The efficacy/adverse effects ratio for this medicinal product is low in this indication.
- There are treatment alternatives which have been better evaluated and are preferred in the guidelines and in practice.
- This proprietary medicinal product has only a very limited role in the therapeutic strategy.

Taking account of these points, the Committee considers that the actual benefit of PHOTOFRIN 75 mg, powder for solution for injection is low in the indication "Treatment of recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment".

The Committee recommends continued inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

011.2 Improvement in actual benefit (IAB)

Based on the current data, PHOTOFRIN does not provide any improvement in actual benefit (level V, non-existent) compared with the currently available therapies in the treatment of recurrent non-small cell lung cancer or oesophageal cancer.

011.3 Target population

There are no epidemiological data that could be used to quantify patients with recurrent non-small cell lung cancer or oesophageal cancer that has had previous locoregional treatment and who may benefit from photodynamic therapy with PHOTOFRIN.

The company has submitted the annual sales data for this proprietary medicinal product in France. The dosage used is 2 mg/kg; it can be assumed that two vials are used in the majority of cases.

From these data, the target population for PHOTOFRIN can be estimated as 20 patients/year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging**

Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.