SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Foscan. This scientific discussion has been updated until 1 January 2005. For information on changes after this date please refer to module 8B.

1. Introduction

Foscan contains temoporfin, a photosensitising agent that is activated with non-thermal light at 652 nm four days after intravenous administration. It is an oncolytic, intended for palliative photodynamic treatment of head and neck squamous cell carcinoma lesions in patients not curable with surgery and/or radiotherapy. The therapeutic effect is mediated through the generation of reactive oxygen species, a process dependent on the intracellular interaction of temoporfin with light and oxygen.

2. Chemical, pharmaceutical and biological aspects

Composition

Foscan is a sterile non-aqueous formulation containing 4-mg/ml temoporfin with ethanol as solvent and propylene glycol as co-solvent. The proposed formulation differs from the formulation used for the majority of the clinical trials in that it does not contain water, since the development programme revealed that water reduces temoporfin stability.
Two pack sizes are proposed, a 3.5 ml vial (corresponding to 14 mg temoporfin) and a 5.0 ml vial (corresponding to 20 mg temoporfin). The primary package for both pack-sizes is a 5-ml amber glass vial sealed with a bromobutyl rubber stopper (West 4023/50/GREY) with aluminium crimp ring. A secondary container of black plastic provides further protection against light.

Active substance

Temoporfin is a photosensitive agent indicated for the photodynamic therapy of certain tumours. Temoporfin is a chlorin, a group that differs from the related porphyrins only in the presence of a centre of saturation. Temoporfin is a single molecule. Temoporfin is well characterised physico-chemically (pKa-values, partition coefficients, solubility in different solvents). NMR, MS, IR, visible and UV spectrum provide evidence of structure. Temoporfin is a dark purple, non-hygroscopic, non-solvated crystalline powder, which is soluble in alcohol/acetone/ethyl acetate and practically insoluble in all aqueous media. Temoporfin exists as a mixture of amorphous and crystalline material with the latter being a single crystal form.

Manufacture of the active substance

Temoporfin is synthesised from non-complex commercially available materials. Crude temoporfin is purified by chromatography. Since the choice of sterilisation of the drug product is by filtration and aseptic fill, it is essential to minimise the bioburden of the active substance. The final steps are therefore conducted after submicron filtration of temoporfin dissolved in ethanol. No catalysts are used in the synthesis. Adequate specifications are given for all starting materials, intermediates, reagents and solvents. Besides the intermediate specifications, in-process control involves the monitoring of impurities during the third stage and the acceptability of the collected eluate fractions before the final stage.

Active substance specifications

The proposed parameters and limits are justified. The parameters listed in the active substance specification are standard pharmacopoeial parameters. For all other impurities the proposed limits are qualified and acceptable. The limits for residual solvents are in accordance or stricter than the ICH guideline Residual solvents. A limit for total viable count is included to confirm the low bioburden.

Stability of the active substance

Basic solutions of temoporfin are not stable and degrade under exposure to light and heat.

Other ingredients

Ethanol, anhydrous and propylene glycol comply with Ph. Eur.

Finished product

The product is manufactured by an aseptic process due to the incompatibility of the product with the normal range of terminal sterilisation methods. The HPLC method used for determining assay and impurities was validated with respect to precision, specificity, sensitivity linearity, robustness and accuracy. The test to determine particulate matter was validated in regard to accuracy, due to the intensity of the colour of the solution. The gel-clot method is performed in accordance with Ph. Eur. The test for lysate sensitivity and absence of interfering factors under test conditions was verified. A sterility test is performed by the direct inoculation method according to Ph. Eur. and was validated as required. The finished dosage form was subjected to light stress testing and to the formal ICH tests at 25 ^{o}C / 60% RH and 40 ^{o}C / 75% RH. The data showed no difference in stability between the two fill volumes. Photostability data conducted according to CPMP/ICH guidelines confirmed that amber coloured glass gives some but insufficient protection to the product. In view of the light sensitivity of the product, it has to be stored in a light opaque secondary container appropriately labelled. A secondary container of black plastic is proposed, providing further protection against light. A shelf life of 2 years ≤ 25 ^{o}C when stored in the secondary container is acceptable.

Both glass and elastomer of the packaging material comply with Ph. Eur. Compatibility studies confirm that the stopper complies with Ph. Eur. requirements for extractables. The level of extractables was performed using USP extraction test with isopropyl alcohol. The results show that stopper residues with vehicle extraction are below that of Ph. Eur. limits for closures.

3. Toxico-pharmacological aspects

Pharmacodynamics

The anti-tumour activity of temoporfin depends on photo-activation with light of 652 nm from a laser. The molecular basis for photodynamic therapy is well understood. The therapeutic effect is mediated through the generation of reactive oxygen species, a process dependent on the intracellular interaction of temoporfin with light and oxygen. Light of 652nm can penetrate tissues to produce meaningful PDT activity at depths of 10-15mm and beyond when the impact of the associated cascade of biological and biochemical events are considered. This implies that Foscan can be used effectively to treat tumours to a depth of 10-15mm from the illuminated surface. For the clinical studies, the dose 0.15 mg/kg was chosen. Intravenous doses in the range of 0.1-0.6 mg temoporfin/kg body weight produced effective tumour necrosis in animal models whilst minimising damage to surrounding normal tissues, provided that the light dose was given between 72-120 hours after administration of temoporfin. Under these conditions, a wavelength of 652 nm, a fluence rate in the range of 50-200 W x cm^{-2}, typically 100 W x cm^{-2} and light doses between 10-20 J x cm^{-2} are appropriate.

Safety studies with the complete final formulation are lacking.

A moderate decrease in pain response at a single dose of 0.5 mg/kg was observed in the mouse Irwin test. Intravenous administration of the vehicle caused transient subdued behaviour in rabbits and was lethal in two animals when the administration rate was 0.5 or 1.0 ml/minute.

In dogs, administration of the vehicle increased arterial blood pressure and showed fluctuations in heart rate and respiratory rate. Two dogs died at 12 ml/minute (24 times the recommended dose rate). The safety of the vehicle as regards respiratory function was satisfactory. In the rat, there was no effect on cardiovascular or respiratory parameters when administering double the clinical dose and double the clinical infusion rate. The administration regimen, both in dogs and in rabbits, was the

predominant factor determining the seriousness of the effects. In rabbits, a dose rate of 0.4 ml/minute was tolerated. In dogs 0.25 ml/kg over 3 minutes was best tolerated. In rats, no adverse effects of temoporfin administration on renal or gastrointestinal function were observed.

Pharmacokinetics

Pharmacokinetics after single intravenous dosing of ^{14}C-temoporfin was studied in mice, rats, dogs and tumour bearing rats. Data on pharmacokinetics after single intravenous administration of unlabelled temoporfin were obtained from toxicokinetic studies in rats, dogs and rabbits performed as part of the toxicity studies, performed under controlled lighting conditions. A delay in tmax was observed, which is atypical for an intravenously administered drug, which might indicate a depot formation in tissues followed by a slow release into the systemic circulation. The results from the pharmacokinetic studies with multiple dosing in rats and dogs showed accumulation of temoporfin in plasma over the dosing period with accumulation ratios of 1.5-2.5 in the 28-day study in rats and 2.4 in the 28-day study with dogs. These ratios are indicative for long elimination half-lives.

Temoporfin exhibited an extensive distribution pattern in the rat, particularly in the liver and also in adrenals, spleen, lungs and bone marrow. No measurable binding of 14C-radioactivity to melanin in pigmented rat eyes or skin could be demonstrated. Release of the drug from the tissues was prolonged, with elimination half-lives in tissues of rat of 16 h, 137 h, 210 h, 227 h, 295 h, 369 h and 489 h in plasma, lung, liver, adrenal, kidney, spleen and muscle, respectively. Several studies in mice and rats showed distribution of temoporfin in tumour tissue. Tumour: tissue ratios were high in skeletal muscle and skin. Protein binding in mouse, rat, rabbit and dog were similar, ranging from approx. 99%. In humans protein binding was lower (approx. 86%). In vitro studies with rat and human liver microsomal preparations did not indicate oxidative metabolism of temoporfin. The excretion/metabolic patterns are very similar in the rat, the rabbit and the dog. Plasma radioactivity up to at least 24 h post-dose was solely associated with the parent compound. Photobleaching, leading to a stable photoproduct of temoporfin appeared an important mechanism to reduce skin levels.

An in-vitro study with human liver tissue did not indicate potential for drug interaction through inhibition of cytochrome P-450 iso-enzymes.

Excretion data in rats and dogs demonstrated that temoporfin is predominantly excreted via the faeces (approx. 70% of the recovered dose). The majority of the dose was excreted within 21 days after dosing, but significant amounts (up to 18%) remained in the carcass. Mass balance studies revealed long elimination half-lives of about 250 h (rats). There were no indications for enterohepatic recirculation.

Toxicology

Single dose toxicity

Single dose toxicity studies were conducted by the intravenous route in mice and rats under normal (~300/343 lux) and subdued (~0/14 lux) light conditions. Animals exposed to normal light conditions showed phototoxicity like swelling and darkening of the skin in exposed areas (tail, abdomen, scrotal sac, ears, eyes and feet). The effects occurred at dose levels $\geq$ 0.85 mg/kg. Systemic toxicity was characterised by changes in haematological parameters (red blood cells, haematocrit and platelets reduced and white blood cells increased) and increased liver and spleen weights. Furthermore, skin inflammation, pycnotic spermatocytes and increased extramedullary haematopoiesis in spleen and the lymph nodes were found. Under subdued light, a low degree of phototoxicity was found only in the highest dose group. Rats appeared more sensitive than mice.

Repeat dose toxicity

Studies of 1-4 weeks duration were conducted in rats and dogs. Rats treated intravenously for 7 days with temoporfin showed severe phototoxicity up to 1 mg/kg/day under normal light conditions and less severe phototoxicity under subdued light conditions. Two weeks intravenous administration of doses of 0.05-0.6 mg temoporfin/kg/day to rats caused inflammatory changes at the injection sites and

swelling/reddening of the tail or ears at 0.3 mg/kg and higher. Rats treated daily intravenously with 0.3 - 1 mg/kg temoporfin for 4 weeks under subdued lighting, showed only an increase of white blood cells at the highest dose level. No signs of phototoxicity were found. In the 2 and 4 weeks studies, rats received a maximum dose of up to 1 mg/kg/day. .
Dogs received doses up to 3 mg/kg/day under subdued light conditions, which provided substantially higher systemic exposure compared to rats. Intravenous administration of temoporfin to Beagle dogs for 14 consecutive days caused dose-dependent inflammation at the injection sites at all doses (0.03 – 0.75 mg/kg/day). A reduction in food consumption was also seen at highest doses. Reddening of the ears, limbs or abdomen, and increased pigmentation in limbs/ears were indicative of phototoxicity of the test drug. In a 4 weeks study in dogs under subdued light conditions severe phototoxic effects were seen. In males, phototoxicity was observed in the pinnae and the prepuce and in females in the area around the vulva, anus, and abdomen. Serious injection site damage was found.

Genotoxicity

Temoporfin did not cause mutations in the Ames test in Salmonella typhimurium strains TA 1535, TA 1537, TA 98, TA 100 and in Escherichia coli WP2uvrA under various light conditions. Furthermore, it did not induce chromosome aberrations or mutations in Chinese hamster ovary cells, or micronuclei in the mouse in vivo. Mutagenic activity with temoporfin was observed in vitro at temoporfin concentrations of 6-16 μg/ml in a mouse lymphoma cell gene mutation test. Under light exposure, temoporfin results in the production of reactive oxygen species. Hence, under these conditions temoporfin may have the potential to be mutagenic. In the clinical situation, the risk may be minimised by avoiding direct exposure of non-tumour tissue to light, and by maintaining patients under the recommended light protection programme.

Carcinogenicity

Carcinogenicity studies were not performed, which is acceptable considering the intended clinical use.

Reproduction toxicity

The effects of temoporfin up to 0.6 mg/kg/day on early embryonic development were investigated in the rat. No obvious signs of maternal or embryo-foetal toxicity were observed (NOAEL 0.6 mg/kg/day). In rabbits, slight maternal toxicity was apparent at the high dose as characterised by reduced food consumption and reduced body weight gain. In the high dose group, an increase in pre-implantation loss and a lower pregnancy rate was recorded, and a decrease in ossification of the occipital skull was observed. Maternal and developmental NOAEL during the organogenesis period was 0.3 mg/kg/day in rabbits. The effects of temoporfin on pre- and postnatal development were investigated in rats. No significant effects were observed that could be related to treatment either in F0 or F1 generation. Maternal, pre-, and post-natal NOAEL was 0.6 mg/kg/day, which does not provide any safety margin compared to the human dose.

Local tolerance

The local tolerance studies in animals are relevant only with respect to the local irritant effects of the solvent. A slight reversible irritancy to rabbit skin was observed. Slight reversible conjunctival redness was seen when temoporfin was applied to rabbit eyes. Intravenous injection of temoporfin solution caused slight to severe erythema, the severity depending on the vehicle used and the amount injected. Propylene glycol/ethanol at the lowest dose tested being slightly less than the clinical dose, caused erythema at the injection site, as well as subdued behaviour on the injection day. The irritation appeared to be somewhat aggravated when temoporfin in solution was injected as compared to injection of vehicle only. Paravenous and intra-arterial injection caused severe erythema, oedema, and mild to moderate subcutaneous inflammation and haemorrhage.

Ecotoxicity/Environmental Risk Assessment

No adverse effects on the environment of the use of temoporfin and its dispersion into the environment are anticipated.

4. Clinical aspects

Clinical pharmacology

Pharmacodynamics

Formal dose finding studies and studies in humans to determine a precise mechanism of action were not conducted. A phase I programme consisting of a series of open uncontrolled investigator sponsored pilot studies in a variety of cancers and other diseases provided the basis for the drug and light dose selected for the Phase II studies. A dose/response relationship has been demonstrated for the dose interval 0.075-0.3 mg/kg with a dose of 0.15 mg/kg found to be effective with acceptable and manageable skin photosensitivity early in the development programme. The recommended light dose 20 J/cm^2 following a drug light interval of 96 hours was required for complete remission of T_{is} to T_4 tumours. Data to demonstrate that the depth of necrosis achieved with the proposed dose, light-dose and drug-light interval at least covers the depth of the tumour was not provided.

Pharmacokinetics

The pharmacokinetics of temoporfin after i.v. injection was evaluated in two pharmacokinetic studies in healthy volunteers and in patients undergoing photodynamic therapy (Table 1). The main difference between the two studies was the solvent used for injection. Additionally, five literature references were included concerning pharmacokinetics in faze I trials in patients.

Distribution

After intravenous injection of a single dose of 0.15 mg/kg, the plasma concentration of temoporfin decreases rapidly. Then after approximately 45 min an increase is observed lasting until C_{max} (about 900-1000ng/ml) is reached after 4 - 8 h, after which the concentration follows a slow bi-exponential decay with a t½ of the initial phase of about 30 hours. The delayed t_{max} was observed both in patients and in healthy volunteers. Such a delay in t_{max} is atypical for an intravenously administered drug and indicates a delay in full distribution of the dose into the systemic circulation. Plasma clearance values are low (about 4 ml/h/kg) demonstrating that temoporfin is a low clearance drug in man. The distribution volume is about 0.5 l/kg, which is between total and extra cellular body water. Temoporfin distributes beyond the blood compartment and exhibits a reasonably extensive distribution in man. Preclinical data showed that several tissues are involved in the uptake of temoporfin. The tissues involved in the uptake of temoporfin in humans have not been investigated. Published data show that temoporfin preferentially concentrates in tumour tissue relative to other tissues. Mean plasma-protein binding ranges around 85-88%.

Table 1: Results of the three pharmacokinetic studies

Parameter	Powder Ethanol/PEG 400/water (2:3:5 v/v) (study 013) healthy volunteers 0.15 mg/kg i.v.	Solution Ethanol/Propylene Glycol 40%/60% (study 018) healthy volunteers 0.15 mg/kg i.v.	Solution Ethanol/Propylene Glycol 40%/60% (study 08b) patients 0.15 mg/kg i.v.
C_{max} (ng/mL)	980 ± 169	861 ± 132	1089 ± 304
t_{max} (h)	8.0 (8.0 – 16.0)	4.0 (2.0 - 8.0)	3.1 (0.2 – 6.1)
$t_{1/2}$ (h)	95 ± 46	88 ± 44	61 ± 24
Clearance (mL/h·kg)	3.1 ± 0.9	3.9 ± 0.9	4.1 ± 1.3
Vd (L/kg)	0.39 ± 0.14	0.46 ± 0.17	0.34 ± 0.11

Metabolism and excretion

The metabolic profile was not identified in humans. Elimination in healthy volunteers is slow. Plasma concentrations decay in a bi-exponential manner with t½ of the initial phase of about 30 hours and a terminal half-life of about 90 hours. A linear relationship between temoporfin systemic clearance and

body weight in animals and humans indicates that total clearance in animals is predictive of that in humans. According to the preclinical studies, temoporfin is metabolised in the liver by conjugation and eliminated in the bile for excretion in faeces. Genetic polymorphism and active metabolites are therefore not of concern and enzyme induction is not an issue with a single treatment modality.

Interaction studies

The effect of Foscan on the cytochrome P450 isoenzymes 2D6 and 3A4 was evaluated in healthy volunteers. A tendency to a reduction in activity for both isoenzymes was observed, however, no conclusive statements could be made due to a large variation. In the clinical studies with temoporfin, a large number of concomitant medications were used including dexamethasone, diclofenac, metronidazole, tramadol, morphine, paracetamol, codeine, fentanyl, and diazepam among the most frequently used. This range includes substrates for CYP's 3A4, 2C9, 2D6, and 2C19, and the glucuronyl transferases. None of the reported adverse events in these studies were attributed to use of concomitant medications, with the exception of one incident with topical 5-fluorouracil where an adverse event arose due to the combined photosensitivity effects of this agent with temoporfin. It is concluded that special warnings regarding potential drug interactions of this nature are not required in the SPC, but a warning is included for topical 5-fluorouracil.

Special populations

A population pharmacokinetic analysis was conducted on 228 patients with head and neck cancer from four studies. These patients were given a single intravenous infusion of 0.15 mg/kg of the Powder for Injection formulation. The estimated clearance and volume of distribution values were in good agreement with those quoted previously. The analysis evaluated any correlated differences in pharmacokinetics with a range of discrete covariates including age, weight, gender, ethnicity, and renal and hepatic insufficiency. No factors were identified that influenced temoporfin pharmacokinetics to the extent that dosage adjustment would be required. This correlates with the lack of clinically significant differences in the adverse event profile in special groups, with the exception of pain, which was chiefly related to the lesion and to PDT. No recommendations for dose adjustment or precaution are therefore necessary in the SPC.

Clinical efficacy

Main clinical studies

The main characteristics of the four pivotal studies are summarised in Table 2. The studies investigated efficacy in 3 different populations. Study 01 concerned primary oral or pharyngeal cancer, studies 03 and 08 primary second or recurrent oral or pharyngeal cancer and the study 08b palliative treatment. These original three indications were later amended to one proposing Foscan-PDT for palliative therapy of head and neck squamous cell carcinoma lesions in patients not curable with surgery or radiotherapy. Thus, the study 08b remained the only relevant study for clinical efficacy.
The primary efficacy parameter in the studies 01, 03, and 08 was histologically confirmed tumour response after both 8 and 12 weeks or in case of slough after both 12 and 16 weeks. The primary efficacy parameter in the study 08b was clinical benefit. All studies included a short-term phase (12/16 weeks) and a long-term follow up phase.

Study 01

This open, uncontrolled, phase II study, was designed to recruit patients with untreated single discrete tumours, easily measured and locally treatable ($T_{is}N_0$, T_1N_0, T_2N_0), with a tumour diameter ≤ 2.5 cm and estimated depth ≤ 0.5 cm, without metastases and not scheduled for neck dissection in continuity, or for neck irradiation. Karnofsky performance status was at least 70%.

Efficacy analysis

Primary efficacy parameter was histologically confirmed tumour complete response to be measured 12 weeks after illumination with response assessment limited to patients with a technically successful PDT-procedure.

Efficacy results

A total of 108 patients were included, all of who received Foscan The median duration of response could not be calculated since loss of local control occurred in less than 50% of the patients. The estimated CR rate at one year is 82% (95% CI: 72%-92%) and at 2 years 75% (95% CI: 63%-88%). Histological response was established in 67 patients with a biopsy, with 55 (82%) patients having no evidence of tumour and 12 patients with evidence of tumour. Seventy-two of the 81 patients with clinical CR were entered into the follow-up study 02, however, no valid conclusion with regard to survival or loss of control can be drawn from the long-term data.

Table 2: Main characteristics of the clinical studies 01, 03 08 and 08b

Study **Design** **Phase** **Country**	**Population characteristics** **(main inclusion and exclusion criteria)**	◦ **Patients planned/analysed** ◦ **Dose** ◦ **Wavelength** ◦ **Fluence Rate** ◦ **Light Dose** ◦ **Response follow-up** ◦ **Long-term follow-up**	**Primary** **Efficacy variable**	**Secondary** **Efficacy variables**
01 OL*, UC Phase IIb UK	Primary SCC of the lip, oral cavity, oropharynx, or hypopharynx; single discrete treatable T_{is-2}, N_0, M_0, depth ≤0.5 mm.	◦ 100-130/106 ◦ 0.15 mg/kg, single treatment ◦ 652 nm ◦ 100 Wcm^{-2} ◦ 20 J ◦ 12 -16 weeks ◦ **Study 02: up to 5 years**	Histological and clinical CR	Tolerability and safety Within **study 02**
03 OL, UC Phase II France	Histologically confirmed recurrent or second primary SCC of the lip, oral cavity, or anterior-2/3 of the tongue, previously treated with RT or surgery, T_{is-2}, N_{any}, M_{any}, depth ≤0.5 mm.	◦ 50/40 ◦ 0.15 mg/kg/treatment with a maximum of 3 retreatments ◦ 652 nm ◦ 100 Wcm^{-2} ◦ 20 J ◦ 12 or 16 weeks ◦ **Study 02: up to 5 years**	CR after 3 treatments	Within **study 02**
08 OL, UC Phase II USA	Histologically confirmed recurrent or second primary SCC of the lip, oral cavity, or anterior-2/3 of the tongue, previously treated with RT or surgery, T_{is-2}, N_{any}, M_{any}, depth ≤0.5 mm.	◦ 50/40 ◦ 0.15 mg/kg/treatment with a maximum of 3 retreatments ◦ 652 nm ◦ 100 Wcm^{-2} ◦ 20 J ◦ 12 or 16 weeks ◦ 2 years	Histological CR after 1-3 treatments	Clinically determined response Duration of CR Survival time Quality of life
08b OL, UC Phase II India, Egypt, Europe, US	Histologically confirmed recurrent, refractory or second primary NHSCC (N_{any}, M_{any}); specific disease related problem or likelihood of significant disease related complication to occur within a short time, both amenable to palliation by Foscan	◦ 50/220 ◦ 0.15 mg/kg/treatment with a maximum of 3 retreatment ◦ 652 nm ◦ 100 Wcm^{-2} ◦ 20 J ◦ 12 or 16 weeks ◦ at least 1 year	Clinical benefit (number/proportion)	Quality of life 1-year survival rate Objective tumour response

*OL: open label; UC: uncontrolled; SCC: squamous cell carcinoma, RT: radiotherapy, CR: complete response

Studies 03 and 08

Studies 03 and 08 concerned patients with recurrent or second primary squamous cell carcinoma of the lip, oral cavity, or anterior two-thirds of the tongue, that were previously treated with radiotherapy or surgery for lesions without nodal or distant metastases (N_0M_0). Karnofsky performance status was at least 70%. Patients could receive a maximum of three treatments with Foscan.

Efficacy results

A total of 41 patients were included in the study 03, of whom 40 received Foscan, and a total of 40 patients were included in the study 08, all of whom received Foscan. Efficacy analysis was restricted to the per protocol population in both studies. Seventeen patients were assessable for tumour response in study 03. Nine patients (53%) had a complete response. The overall response rate was 59%. Twelve patients entered the long term follow up phase of whom nine had a clinical complete response. Duration of response ranged from 61-452 days.

Twenty-eight patients with a total of 30 lesions were assessable for response in study 08. There was a histologically confirmed response rate by lesion of 53% in the per protocol population. The overall complete response rate by lesion was 63% and the overall response rate by lesion 73%. Seventeen patients entered the follow up phase, and at the cut off point, no patients had reached the one-year assessment point. Duration of response ranged from 55-625 days. Three patients with biopsy confirmed complete response had recurrences with a median time to recurrence of 171 days. Mean survival times were 570 days (range 35-551days) for study 03, and 520 days (range 12-680 days) for study 08. No valid conclusions with regard to survival or loss of control can be drawn from the long-term data.

Karnofsky performance index was scored at baseline and at week 12/16 in both studies. Taken together, Karnofsky performance index did not differ between baseline and at the end of the short-term phase.

Study 08b

This was a multicentre study conducted in India (72 patients), Europe (53 patients), USA (17 patients) and Egypt (5 patients). The sites of the primary tumours were buccal mucosa, tongue, floor of the mouth, larynx and tonsil. The primary endpoint of the open label, single group, single and multiple dose study was the individual clinical benefit gained from palliative treatment with Foscan-PDT in the management of recurrent, refractory or second primary neck and head squamous cell cancer (HNSCC) in patients for whom surgery or radiotherapy was considered inappropriate and in whom palliation of a specific disease related problem were possible. The tumour response was a secondary endpoint.

Efficacy analysis

The primary efficacy parameter was the change in a prospectively defined key symptom (pain, eating including swallowing and chewing, disfigurement, and speech), to be measured with the University of Washington Head & Neck Questionnaire (UWHNQ), or prevention of a complication of advanced HNSCC (objective response). Objective improvement was defined as normalisation or improvement of at least 2 grades in the severity assessment of the key symptom or prevention of an expected complication (prevention of perforation of a fistula, fungation, disintegration of tracheostomy). Secondary efficacy parameters were improvement in global, functional and symptomatic measures of QoL, objective tumour response (complete and partial), one-year survival rate, Karnofsky Performance Index, and tolerability and safety. The study period for short-term efficacy consisted of 12/16 weeks. After completed treatment, all patients were to be followed-up for 1 year for duration of palliative benefit, tumour response and survival.

Previous surgical and radiotherapy treatments received by patients in Indian and EU/US centres are shown in Table 3.

Table 3: Summary of prior therapy

	Number of patients		
	All Centres N=147	**Indian/Egyptian N=77**	**European/US N=70**
Surgery	71%	75%	66%
Radiotherapy	90%	90%	90%
Chemotherapy	41%	42%	40%

Efficacy results

A total of 220 patients were enrolled, of which 196 were treated with Foscan. At the time of database cut-off 49 patients were still on study, but had not completed the 12/16-week treatment observation phase. The 12/16 weeks data as considered for the ITT analysis included 194 treatments in 147 patients. The patient population was divided into 128 patients in whom the primary aim was tumour shrinkage and symptom reduction and 19 patients in whom the aim was prevention of a complication.

Symptomatic benefit was assessed using the following key items from the UWQOL questionnaire:

- Pain (0 – 4, none – severe pain not controlled by medication)
- Eating-Swallowing (0 – 3, no problem – I cannot swallow)
- Eating-Chewing (0 - 2, no problem – I cannot even chew soft solids)
- Disfigurement (0 – 4, no problems – I cannot be with people due to my appearance)
- Speech (0 – 4, no problem – I cannot be understood)

Symptomatic response was defined by at least a two-grade reduction, or normalisation of a prospectively defined symptom as scored by the patient. Altogether 28/128 of the patients fulfilled these criteria. Fifty percent of these patients reported normalisation or a two-grade reduction of any of the five UWQOL symptom scores. Duration of protocol defined symptomatic response was calculated from the visit at which response was first noted to the last visit at which response was recorded and was found to have a mean 44 days and a median of 21 days.

Tumour response was observed in overall 37/147 (25%) of the patients after the first treatment course. Further details are presented in table 4 below.

Table 4: Patient disposition and tumour response (Best Response, WHO, ITT)

Treatment course Number of patients Response data	Discontinued during the 12/16-week evaluation period	Patients entering 1-year follow-up Response characteristics	Discontinued during 1-year follow-up	Still on study (October 2000)
1 147 20 CR 17 PR 62 NC/PD 57 Non-evaluable/ Unknown Mean R duration 105 d Median 57 d Mean CR dur.. 122 d Median 70 d	60 death 46 progression 4 lost to FU 3 non-compliant 5 withdrawn 2	50 17 CR 4 PR 20 NC/PD 9 Non-evaluable/ Unknown	23 death 16 lost to FU 4 withdrawn 3	27 12 CR 3 PR 8 NC/PD 4 Non-evaluable/ Unknown
2 37 6 CR 4 PR 14 NC/PD 13 Non-evaluable/ Unknown Mean R duration 55 d Median 55 d Mean CR dur. 54 d Median 28 d	13 death 10 progression 1 lost to FU 1 non-compliant 1	15 5 CR 1 PR 6 NC/PD 3 Non-evaluable/ Unknown	6 death 5 progression 1	9 1 CR 0 PR 5 NC/PD 3 Non-evaluable/ Unknown
3 9 0 CR 0 PR 3 NC/PD 6 Non-evaluable/ Unknown	8 death 6 non-compliant 2			
4 1 1 NC/PD				1 1 NC/PD

In the appeal documentation, further analyses were conducted aiming at identifying baseline factors of importance for tumour response. These analyses focused on patients treated with the aim of symptom reduction (n=128). This approach does not inflate response data as there were 4 CR in the group of patients (n=19) excluded from further analysis.

Twenty-five patients died and 8 patients were withdrawn prior to the first assessment of tumour response and altogether tumour mass reduction measurements are missing for 36/128 patients. In a total of 102 lesions, at least one response assessment was available allowing an analysis relating tumour mass reduction to tumour depth (Table 5).

Table 5: Proportion of lesions achieving tumour mass reduction by tumour depth

% tumour mass reduction	All lesions N=102	≤10 mm N=52	10 to ≤ 20 mm N=31	>20 mm N=19
100	44 (43%)	31 (60%)	9 (29%)	4 (21%)
≥50	59 (58%)	39 (73%)	15 (48%)	5 (26%)
≥25	66 (65%)	39 (75%)	18 (58%)	9 (47%)

Although the data presented in Table 5 may derive from only one tumour mass assessment and they are presented per lesion, it appears reasonable to conclude that tumour depth is of importance for tumour response.

Completeness of illumination was determined by using the surface area of each lesion and the illumination spot diameter. If the illumination spot area was greater or equal to the tumour area, illumination was categorised as complete. Of the 128 patients treated for palliation, 95 patients with 112 lesions were judged to have received complete illumination (Table 6).

Table 6: Proportion of lesions achieving tumour mass reduction by completeness of illumination

% tumour mass reduction	All lesions N=102	Complete N=82	Incomplete N=20
100	44 (43%)	41 (50%)	3 (15%)
≥50	59 (58%)	51 (62%)	8 (40%)
≥25	66 (65%)	55 (67%)	11 (55%)

These results should be interpreted with caution, as large tumours are more likely to be incompletely illuminated than small tumours. This may be illustrated by the fact that 7/19 tumours with a depth >20 mm (5/7 ≥30 mm) were incompletely illuminated vs. 13/83 with a depth ≤ 20 mm.

The appeal documentation included also the results for all patients with a tumour depth ≤ 10 mm and completely illuminated, non-externalising lesions ("optimal patients"). There were altogether 43 patients fulfilling these criteria and the overall response rate (WHO) was 40% (10 CR, 17 PR).

The assessment of duration of tumour response was not a primary endpoint of the protocol. Due to loss of patients from the study (mainly through death) and to tumour necrosis, sloughing and healing, the duration of response was difficult to estimate. Duration was calculated from the visit at which response was first recorded to the last visit at which response was noted. Mean duration (SD) of overall response was 108 (107) days and for patients obtaining complete response 145 (145) days.

Clinical safety

Patient exposure

The safety population consisted of 855 persons (811 patients, 44 volunteers) with 1064 treatments. These included data from the Integrated Safety Population from the four submitted studies in head and neck cancer (ISP, n=314), an additional phase II study 06 in patients with superficial epidermoid carcinoma of the oesophagus, oral cavity, pharynx, larynx, trachea and bronchi (n=47), as well as an extensive Expanded Access Programme which allowed named-patient treatment with Foscan-PDT over a wide range of malignant and other conditions (n=450), and in human volunteers (n=44). During the assessment procedure, the Applicant submitted an update on study 08b, thereby extending the number of patients from 64 (efficacy)/99 (safety) to 147 patients. The assessment of clinical safety was based on the originally submitted data.

Adverse events and serious adverse events/deaths

Table 7 summarises the adverse events in the ISP (consisting of all four pivotal studies) and study 08b. The majority (79%) of adverse events in the ISP were at least possibly related to treatment. The differences in incidences between study 08b and the IPS population showed that most adverse events were reflecting the site and stage of the disease. The most common adverse events in the IPS population were facial pain, pain and mouth necrosis. The most common adverse events in study 08b were injection site pain, haemorrhage and dysphagia. After exclusion of injection site pain, the vast majority of adverse events occurred during or after the illumination. Besides pain in the face, the adverse events were mild to moderate. Pain in the face was associated with treatment of the tumour. All patients who receive Foscan will become temporarily photosensitive and must observe precautions to avoid sunlight and bright indoor light. Most toxicity associated with this therapy are transient local effects seen in the region of illumination and occasionally in surrounding tissues. There is transient neutrocytosis due to the tumour necrosis and acute inflammatory

response, and a clinically insignificant drop in haemoglobin concentration has been observed which may persist for 3 months.

Phototoxicity

All patients who receive Foscan will become temporarily photosensitive and must observe precautions to avoid sunlight and bright indoor light. Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. In the global safety database, the pattern of photosensitivity reactions shows a maximal incidence around the day of illumination. Fifty-seven % of photosensitivity events were reported in the first 15 days, 11% in the following week, and 13% in the week thereafter. In 170 patients, 176 photosensitivity adverse events were reported, including 19 severe reactions. The overall incidence of serious phototoxicity is 1.6%. Special attention is paid to the phototoxicity events in a phase I study in volunteers. All volunteers in this study (n=14) experienced a photosensitivity reaction with 7 classified as serious adverse event. Most events occurred on or after day 15. The cause of events in the study was investigated thoroughly and was almost certainly related by insufficient compliance with the light avoidance instructions and procedures and not to the formulation. Precautionary measures in the event of suspected extravasation of Foscan are included in the SPC, which should minimise or prevent localised phototoxicity.

Laboratory findings

The most common adverse event was transient increase in white blood cell count observed during the first 1-2 weeks after treatment. This was expected due to the tissue necrosis induced by the treatment. This adverse event was of no clinical significance. In study 01 and 03 an elevation in platelet count was noted although of no clinical significance. A mean fall in haemoglobin of 0.5 g/dl, enduring for the entire follow-up and also occurring in volunteers (who received Foscan, but no PDT), was very modest in almost all patients. Moreover, serum creatinine and urea rose appreciably (respectively 18 and 20%) which was likely to be a consequence of dehydration due to oral discomfort.

Cardiovascular effects

These were limited to a few patients with hypo- or hypertension of moderate severity or negative re-challenge.

Table 7: Summary of adverse events with an incidence of ≥ 5% categorised according severity

Adverse Event	Study 08b (N=99)								Integrated Safety Population (N=314)							
WHO Preferred Term	Total		Mild		Moderate		Severe		Total		Mild		Moderate		Severe	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Injection site pain	14	14.1	3	3.0	8	8.1	3	3.0	23	7.3	8	2.6	11	3.5	4	1.3
Haemorrhage NOS	13	13.1	8	8.1	2	2.0	3	3.0	17	5.4	11	3.5	3	1.0	4	1.3
Dysphagia	11	11.1	3	3.0	6	6.1	3	3.0	19	6.1	7	2.2	9	2.9	5	1.6
Infection localised	11	11.1	7	7.1	4	4.0	0	0.0	19	6.1	9	2.9	10	3.2	0	0.0
Face oedema	10	10.1	2	2.0	6	6.1	2	2.0	29	9.2	8	2.6	16	5.1	6	1.9
Pain in face	10	10.1	6	6.1	8	8.1	2	2.0	156	49.7	57	18.2	95	30.3	43	13.7
Constipation	9	9.1	3	3.0	7	7.1	0	0.0	30	9.6	15	4.8	15	4.8	2	0.6
Vomiting	9	9.1	6	6.1	2	2.0	1	1.0	21	6.7	14	4.5	5	1.6	2	0.6
Anaemia	8	8.1	7	7.1	0	0.0	1	1.0								
Scar	8	8.1	1	1.0	5	5.1	2	2.0	22	7.0	9	2.9	10	3.2	3	1.0
Mouth ulceration	7	7.1	5	5.1	2	2.0	0	0.0								
Pain	7	7.1	4	4.0	4	4.0	0	0.0	47	15.0	20	6.4	28	8.9	8	2.6
Insomnia	6	6.1	2	2.0	4	4.0	0	0.0								
Mouth necrosis	6	6.1	3	3.0	3	3.0	1	1.0	37	11.8	17	5.4	18	5.7	5	1.6
Diarrhoea	5	5.1	2	2.0	2	2.0	1	1.0								
Oedema	5	5.1	2	2.0	2	2.0	1	1.0								
Nausea	5	5.1	2	2.0	2	2.0	2	2.0	29	9.2	19	6.1	5	1.6	6	1.9
Swallowing difficult	5	5.1	3	3.0	1	1.0	1	1.0	16	5.1	7	2.2	7	2.2	2	0.6
Trismus	5	5.1	0	0.0	5	5.1	0	0.0								
Photosensitivity reaction									17	5.4	10	3.2	10	3.2	3	1.0
Sunburn									17	5.4	13	4.1	4	1.3	0	0.0
Total	154		69		73		23		499		224		246		93	

% based on number of patients in the population

Since one patient may have had adverse events with several severities, row totals may be higher than the column "total"

Table 8: Summary of deaths and serious adverse events in patients in the global safety population

Population	08b Safety (N=99)		08b Efficacy (N=64)		Studies 01/03/08 (N=215)		ISP (N=314)		06 (N=47)		00 (N=450)		Total (N=811)	
Deaths	**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**		**n (%)**	
- All	65 (66)		41 (64)		38 (18)		103 (33)		4 (9)		22 (5)		129 (16)	
- Attributable to treatment	1 (1)		0 (0)		0		1 (0.3)		0		4 (1)		5 (1)	
- Disease progression	55 (56)		35 (55)		19 (9)		74 (13)		1 (2)		9 (2)		84 (10)	
- Other	9 (9)		6 (9)		19 (9)		28 (9)		3 (6)		9 (2)		40 (5)	
Non-fatal SAEs	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
- All	19 (19)	34	13 (20)	21	69 (32)	91	88 (28)	125	14 (32)	17	70 (16)	87	172 (21)	229
- Attributable to treatment	6 (6)	9	4 (6)	6	15 (7)	17	21 (7)	26	5 (11)	6	37 (8)	39	63 (8)	71
- Other	15 (15)	25	10 (16)	15	58 (27)	74	73 (23)	99	9 (19)	11	40 (9)	48	122 (15)	158

ISP = Integrated Safety Population (Studies 01/03/08/08b)
N = Total number of patients in population; n = No. of patients in subgroup
E = No. of events

Note: For non-fatal SAEs, patients may have more than one event and therefore can be listed under ‘attributable to treatment’ and ‘other’

Local effects

Injection site reactions occurred frequently but were insignificant as long as no extravasation occurred. One patient developed post-inflammatory hyperpigmentation. The local adverse reactions probably represent an acute tissue inflammatory response induced by photo-activation. There may be transient pain during injection, which can be reduced by slowing the infusion rate. There may be pain due to tumour necrosis, which may require the use of NSAIDs or other oral analgesics for 2-3 weeks following treatment.

Table 8 summarises the deaths and non-fatal serious adverse events in the global safety population. One originally treatment-attributed death (carotid artery blow-out) in study 08b was reviewed by the Palliative Assessment Panel, who considered the death as unlikely attributable to treatment. The remaining treatment-attributed death concerns a cardiovascular accident as a consequence of sudden haemorrhage from the right carotid artery. The other 4 deaths were not related to the currently requested indication, or not treated in accordance with the currently proposed parameters. In total, there were 229 non-fatal serious adverse events reported in 172 Foscan-PDT treated patients from all studies in the global safety database. Of these, 71 events were considered as attributable to treatment, occurring in 63 patients. Treatment related deaths were very rare (<1%).

Safety in special populations

Analyses by demographic sub-populations (age, sex, race, weight, hepatic function, renal function) did not reveal any influence on the incidence of adverse events, with the exception of pain in the face, which occurred more frequently in white patients compared to Asian patients.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of the product is considered acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. An in-line filtration should be obligatory during administration of Foscan and an in-line filter set-up assembly included in the package, since visual checks for particulates are not possible. Moreover, the administration set to be used for the administration of Foscan should be compatible with the vehicle of the product due to the non-aqueous solvents (ethanol, propylene glycol) present.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies indicate that by controlling light dose, light wavelength, time interval to light exposure as well as drug dose, the appropriate anti-tumour activity is obtained. There is some uncertainty as to the safety pharmacology of the complete formulation of Foscan at dose volumes and rates above the clinically recommended volume and rate, since the applied doses were not in excess of the human therapeutic dose to provide an adequate margin of safety. There is also an ambiguity as to whether relevant human metabolites are toxicologically tested in the animal models. The toxicology programme revealed that temoporfin, due to the generation of reactive oxygen species, poses a minor risk of mutagenicity, which should be acceptable due to the restricted nature of the target population. Local tolerance studies showed that the proposed formulation of Foscan was irritating. A slow rate of administration and special care to prevent extravasation is of great importance.

Efficacy

Studies 01, 03 and 08 were not considered adequately designed to support the broad indication initially applied for " … treatment of primary, second primary, recurrent or refractory squamous cell carcinoma..". The indication was therefore restricted at this stage to patients with advanced disease. Due to concerns related to methodology and patient benefit, Foscan was initially not recommended for

licensing. Based on new analyses provided in the appeal procedure, these issues have been reassessed by the CPMP and at an expert group meeting.

The pivotal study (08b) designed to support the indication "palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or chemotherapy" was a non-comparative study. Data to support this indication should, however, ideally derive from a randomised, best supportive care comparative study. This was discussed during the expert meetings and the proposed controlled study by EORTC to was not considered feasible due to insufficient inclusion of patients. A chemotherapy-comparative, superiority study was also discussed as a possible alternative. Due to difference in side effects and therefore likely difference in target populations in clinical practice and the problems seen in general when very different treatment modalities are compared, this was not considered to be a fully valid alternative. The uncontrolled nature of the pivotal study was therefore judged to be acceptable.

The heterogeneity of the patient population in the pivotal study was also discussed and it was concluded that it was representative for later stage head and neck cancer patients. Heterogeneity with respect to anatomical localisation is unlikely to be associated with different biological properties with respect to sensitivity to photodynamic therapy. Available subgroup efficacy analyses related to localisation of the tumour support this view.

In the initial evaluation there were concerns raised as to the decision whether the patient was incurable by surgery or radiotherapy was made solely by the treating physician, instead of a multidisciplinary team. Possible differences in local therapeutic facilities were also a matter of concern. In the course of the appeal procedure, however, the Applicant clarified that all patients enrolled in the study were treated in oncology centres, which as a standard practice involved a multidisciplinary team in therapeutic decisions. Moreover, it was concluded that for the assessment of antitumour activity it is more important that base-line co-variates of possible relevance for antitumour activity such as prior radiotherapy are similar, than if alternative treatment options were excluded according to particular standards.

The palliative aims of the treatment, i.e. reduction and deterrence of tumour related symptoms, are fully recognised by the CPMP. Nevertheless, due to the absence of a concurrent control, the 3-week interval between symptom scoring, the potentially distorting effects of missing data and the very advanced stage of disease in a large proportion of patients, the Expert group and the CPMP during their discussions found it reasonable to put more weight on tumour response data. The tumour response rate after one treatment course (overall 26%), higher in patients with a tumour depth less than 10 mm, and a response duration of median two, mean three months were found to be of clinical interest for selected patients with late-stage head and neck cancer without available treatment options. In the trial, a large proportion of patients also had a too large tumour burden to be likely to benefit given the physical restrictions of photodynamic therapy. In this context, taking the methodological issues discussed above into account, a symptomatic response rate of 22% with respect to a pre-specified symptom and 50% overall, is not without interest. The short documented duration of symptomatic response, mean 6 weeks, however, is a concern. Confirmatory data from a more properly selected group of patients were therefore considered essential.

The Applicant has committed to perform post-marketing studies to confirm the efficacy of the product in the proposed indication. The CPMP will be consulted through the Scientific Advice Review Group for the design of the studies.

Safety

The safety database for Foscan contains 855 persons with 1064 treatments including early and advanced stages of head and neck cancer, oesophagus, trachea and bronchial cancer as well as healthy volunteers. The product has an acceptable safety profile, if used in experienced hands and the necessary infrastructure is available. The adverse effects mainly relate to local effects of tumour necrosis with pain and dysphagia reported in 10 and 4% of the patients respectively. The risk of phototoxicity is acceptable if the precautionary measures described in the SPC are adhered to.

Benefit/risk assessment

At the end of the appeal procedure the majority of the CPMP members were of the view that temoporfin PDT has an overall positive benefit/risk ratio for the treatment of patients with head and neck cancer in the palliative setting. However, six CPMP members had a divergent opinion. They were of the view that the available phase II study showed major deficiencies regarding design and that the duration of response observed in this study cannot be considered as of sufficient clinical relevance.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Foscan was favourable. As a result the CPMP recommended the granting of the marketing authorisation under exceptional circumstances for this medicinal product in the following indication: "Foscan is indicated for the palliative treatment of patients with head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy."