European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 12 June 2007
Doc.Ref.: EMEA/248362/2007

Dr. Wassil Nowicky
Now Pharm AG
241, route d'Arlon
L-1150
Luxembourg

RE: EMEA/OD/002/07
COMP/234369/2007
Chelidonii radix special liquid extract, Now Pharm AG

Dear Dr Nowicky,

Pursuant to Article 5 of Regulation (EC) No. 141/2000 of 16 December 1999, please find enclosed the negative opinion of the Committee for Orphan Medicinal Products on chelidonii radix special liquid extract, in the indication of treatment of pancreatic cancer, as adopted in English by the Committee on 31 May 2007. The EMEA/COMP Summary Report adopted by the Committee is also enclosed for your information.

Please inform the EMEA in writing within 15 days of the receipt of the opinion if you intend to appeal. In accordance with Article 5.7 of Regulation (EC) 141/2000 detailed grounds for the appeal must be sent to the EMEA within 90 days of the receipt of the opinion.

Please acknowledge the receipt of this letter immediately in writing. Should you have any query on the enclosed please do not hesitate to contact Ms Frida Rivière (ext. 7039), or her secretary, Cinzia N'Diamoi (ext. 8456).

Yours sincerely,

Prof. Spiros Vamvakas
Acting Deputy Head of Sector Scientific Advice and Orphan Drugs

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 8400 Fax (44-20) 75 23 70 40
E-mail: orphandrugs@emea.europa.eu www.emea.europa.eu

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/COMP/234369/2007
EMEA/OD/002/07

OPINION OF THE COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS ON ORPHAN MEDICINAL PRODUCT DESIGNATION

Medicinal product

Active ingredient:	Chelidonii radix special liquid extract

Sponsor

Name or corporate name of sponsor:	Now Pharm AG
Permanent address of sponsor:	241, route d'Arlon L-1150 Luxembourg

Indication

Orphan indication:	Treatment of pancreatic cancer

Basis for opinion

Pursuant to Article 5 of Regulation (EC) No 141/2000 of 16 December 1999, Now Pharm AG submitted to the EMEA on 6 February 2007 an application for orphan medicinal product designation for the above-mentioned medicinal product.

The procedure started on 5 March 2007.
Written explanations were provided by the sponsor on 15 May 2007.
Oral explanations were given by the sponsor on 31 May 2007.

Opinion

1. The COMP, having considered the application in accordance with Article 5 of Regulation (EC) No 141/2000 of 16 December 1999, is of the opinion that:
   - the medicinal product does not satisfy the criteria for designation as set out in the first paragraph of Article 3(1)(a), Regulation (EC) No 141/2000 of 16 December 1999;
   - the sponsor has not established, as required under Article 3(1)(b), Regulation (EC) No 141/2000 of 16 December 1999, that the above-mentioned product will be of significant benefit to those affected by the condition in question for which a satisfactory method of treatment has been authorised in the Community.

   The COMP, therefore, recommends, by consensus, the refusal of the orphan medicinal product designation for the above-mentioned medicinal product in respect of the above-mentioned indication.

2. The grounds for the opinion on orphan medicinal product designation are set out in Annex I.

This opinion is forwarded to the European Commission and to the sponsor, together with its annex.

London, 31 May 2007

On behalf of the COMP
Dr Kerstin Westermark
Chairperson

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 40
E-mail: orphandrugs@emea.europa.eu www.emea.europa.eu

ANNEX I

GROUNDS FOR THE OPINION ON ORPHAN MEDICINAL PRODUCT DESIGNATION

GROUNDS FOR THE OPINION ON ORPHAN MEDICINAL PRODUCT DESIGNATION

The sponsor, Now Pharm AG, submitted on 6 February 2007 an application for designation of a medicinal product containing chelidonii radix special liquid extract as an orphan medicinal product for treatment of pancreatic cancer.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- Pancreatic cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening due to a very poor overall survival;
- satisfactory methods of treatment of the condition have been authorised in the Community, and the sponsor has not provided sufficient justifications that chelidonii radix special liquid extract may be of significant benefit to those affected by the condition, over currently authorised treatments for pancreatic cancer, neither through better efficacy, better safety, or a significant contribution to patient care.

The Committee for Orphan Medicinal Products has recommended the refusal of the granting of the designation of chelidonii radix special liquid extract as an orphan medicinal product for treatment of pancreatic cancer.

European Medicines Agency
Evaluation of Medicines for Human Use

London, 31 May 2007
EMEA/COMP/96936/2007 Final

EMEA/COMP SUMMARY REPORT

on an application

for Orphan Medicinal Product Designation

Chelidonii radix special liquid extract

EMEA/OD/002/07

Sponsor: Now Pharm AG

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: orphandrugs@emea.europa.eu http://www.emea.europa.eu

PRODUCT INFORMATION

Active substance:	Chelidonii radix special liquid extract
International Nonproprietary Name:	
Proposed Tradename:	Ukrain
Sponsor:	Now Pharm AG 241, route d'Arlon L-1150 Luxembourg
Pharmaco-therapeutic group (ATC Code):	L01C
Orphan indication:	Treatment of pancreatic cancer
Pharmaceutical form(s):	Solution for injection
Route(s) of administration:	Intramuscular use

TABLE OF CONTENTS

I ADMINISTRATIVE DATA

The sponsor Now Pharm AG - Luxembourg submitted on 6 February 2007 an application for designation as an orphan medicinal product to the European Medicines Agency (EMEA) for chelidonii radix special liquid extract for treatment of pancreatic cancer.

The sponsor argued that Chelidonii radix special liquid extract will be of significant benefit over the authorised medicinal products to those affected by the condition.

- The COMP Co-ordinator and experts for the application were appointed at the COMP Meeting on 9-10 January 2007:
  COMP Co-ordinator: Dr Katerina Kubácková
  EMEA Co-ordinator: Dr Paolo Tomasi
  COMP Expert: Prof. Hans Winkler

- A pre-submission meeting was held on 14 December 2006.

- Date of start of procedure: 5 March 2007.

- Date of circulation of draft Summary report to COMP: 2 April 2007.

- The application was discussed by the COMP on 11-12 April 2007. Following this COMP meeting, a request for written explanation/oral explanation was sent to the sponsor on 16 April 2007.

- Supplemental information was provided by the sponsor on 15 May 2007. An oral explanation was made by the sponsor on 31 May 2007.

- During the meeting on 30-31 May 2007 the COMP, in the light of the overall data submitted and the discussion within the Committee, issued a negative opinion by consensus on orphan medicinal product designation for Chelidonii radix special liquid extract on 31 May 2007.

Current regulatory status and marketing history:

The product was not authorised in any country inside or outside the EU at the time of submission of the application.

Two applications for marketing authorization were filed in Austria. Both were rejected, the latest in 2002.

Chelidonium majus alkaloids derivate with ThioTEPA has been approved in the following countries: Belarus (1995, reg. #1330/95), Ukraine (1998, reg. #3641), Georgia (1999, reg. #002861), Turkmenistan (2000, reg. #0001707), Azerbaijan Republic (2000, reg. #00267), and Tajikistan (2000, reg. #000568).

In the USA orphan drug status was granted on 20 August 2003 for treatment of pancreatic cancer.

In Australia orphan drug status was granted on 8 June 2004 for treatment of pancreatic cancer.

II BACKGROUND ON THE PRODUCT

1. Proposed indication

Chelidonii radix special liquid extract is proposed for the treatment of pancreatic cancer.

2. Main features of disease/condition

Pancreatic cancer represents the 4th to 5th leading cause of cancer-related death in Europe, Japan and the US, with 30,000 deaths estimated in the US. The disease is difficult to diagnose in its early stages, and more than 80% of the patients die from the disease within one year from the diagnosis. Similarly

to 15 years ago, the overall 5-year survival rate for the disease is less than 5% (Jemal 2005). Nonmetastatic, locally advanced disease is associated with an average survival of 6-10 months. Median survival for patients with metastatic pancreatic cancer is 3-6 months.

Classification

Pancreatic cancer can arise from both the exocrine and endocrine portions of the pancreas. Of pancreatic tumours, 95% develop from the exocrine portion including the ductal epithelium, acinar cells, connective tissue, and lymphatic tissue.

About 5% of pancreatic tumours are actually pancreatic neuroendocrine tumours (such as insulinomas.) These generally have a more favourable prognosis, but that will not be further analyzed here. Instead, this orphan drug application concerns the remaining 95% of pancreatic tumours, which are classified as "malignant" or "borderline malignant" pancreatic adenocarcinomas.

The first class ("malignant") comprises duct cell carcinoma (90% of all cases), acinar cell carcinoma, papillary mucinous carcinoma, signet ring carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, mucinous carcinoma, giant cell carcinoma, mixed type (ductal-endocrine or acinar-endocrine), small cell carcinoma, cystadenocarcinoma (serous and mucinous types), pancreatoblastoma papillary-cystic neoplasm (Frantz tumours), and invasive adenocarcinoma associated with cystic mucinous neoplasm or intraductal papillary mucinous neoplasm. "Borderline" malignancies comprise mucinous cystic tumours with dysplasia, intraductal papillary mucinous tumours with dysplasia and pseudopapillary solid tumours (Evans et al, 2004.)

Etiology and pathology

The causes of pancreatic cancer are poorly understood, and only a limited number of demographic, environmental, risk and genetic factors are associated with the disease. Overall, estimates indicate that 40% of pancreatic cancer cases are sporadic in nature. Another 30% are related to smoking, and 20% are associated with dietary factors. Only 5-10% are hereditary in nature. Fewer than 5% of all pancreatic cancers are related to underlying chronic pancreatitis (Erickson 2006).

Approximately 75% of all pancreatic cancers occur within the head or neck of the pancreas, 15-20% occur in the body of the pancreas, and 5-10% occur in the tail. Typically, pancreatic cancer first metastasizes to regional lymph nodes, then to liver, and less commonly, to the lungs. It can also directly invade surrounding visceral organs such as the duodenum, stomach, and colon.

Approximately 90% of pancreatic cancers are already metastatic when diagnosed. In about 80%, liver metastases are detectable in addition to metastases in the duodenum, retroperitoneum and lymph nodes.

Symptoms

Pancreatic carcinoma is a fatal disease in the vast majority of patients. Typically pancreatic cancer initial symptoms are vague and include weight loss, fatigue, anorexia, non-specific gastrointestinal symptoms and depressed mood.

These subtle clinical symptoms are often unnoticed until the appearance of jaundice and pain in the upper abdomen. This usually leads to diagnosis of pancreatic cancer at a time when the disease is advanced to a degree that it is unresectable, and the long term benefits of chemotherapy and radiation therapy are limited (Hawes 2000).

Even with surgery, patients often have poor long-term survival due to the propensity of the disease to relapse. Significant risk factors for recurrence include node-positive disease and involved surgical margins.

3. Active substance and pharmacological class and mode of action

Chelidonium majus (greater celandine) is used for the production of extracts which are ingredients of many herbal medicinal products from the groups cholagoga and bile duct therapeutics, for example Aristochol®, Chelidophyt®, Cholagogum N Nattermann®, Cholarist®, Esberigal®, Gallopas® 100, Horvilan®, Panchelidon®, Zettagall® V etc. The active substance of the herbal remedies and extracts are alkaloids. Chelidonine is the main alkaloid of *Chelidonium majus*.

"Chelidonii radix special liquid extract" is a product that results from a treatment of alkaloids from *Chelidonium majus* with Thio-TEPA in the presence of hydrochloric acid. The other names used in this summary to describe the product are "Ukrain" and NSC 631570 (National Cancer Institute code).

Chelidonine, like some other *Chelidonium majus* alkaloids, is hardly soluble in water. This makes intravenous injections impossible. The special extract is manufactured in a multi-step procedure, starting with the ethanolic extraction of greater celandine roots. The crude extract is purified and then processed with hydrochloric acid and thiotepa BP.

The result of this process is a precipitate, which might be unstable and hygroscopic. Therefore it is immediately purified and then dissolved in water for injection (33 mg/ml). This solution is the drug substance "Chelidonii radix special liquid extract".

The final herbal medicinal product (Ukrain) contains a sterile aqueous dilution of "Chelidonii radix special liquid extract" in a concentration of 0.0303 ml per ml finished product, according to 1 mg solid substance per ml. Sodium hydroxide solution and hydrochloric acid are used to adjust the pH value of the solution (3.0 – 5.5).

According to data submitted by the sponsor in previous applications, the following tertiary alkaloids may be contained in the end product: chelidonine (main component), protopin, stylopin, allocryptopin, a-homochelidonine, chelamidine, chelamine, L-sparteine, chelidimerine, dihydrosanguinarine, oxysanguarine, oxychclidonine and methoxychefidonine.

Thio-TEPA is listed in many pharmacopoeiae (e.g. UK, Japan, France, USA) and is approved as a cytostatic in Austria. No free Thio-TEPA or aziridine ring compounds can be detected in NSC 631570. Ukrain is therefore definitively different from the starting materials.

According to the Sponsor, the National Cancer Institute determined that NSC 631570 (the abbreviation given to Chelidonii radix special liquid extract by the National Cancer Institute) has a completely different effect on malignant cells compared to Thio-TEPA (NSC 6396) or chelidonine hydrochloride (NSC 406034).

Chelidonii radix special liquid extract lead to a significant accumulation of cells in G2/M phase in all investigated cell lines, and also determined a significant reduction of proliferation rates after 48 hours. Fluorescent immuno-histochemistry with antibodies against alpha-tubulin revealed that Chelidonii radix special liquid extract and chelidonine lead to a disruption of the microtubule network in the investigated cell lines. Furthermore, *in vitro* polymerisation assays showed that both agents stabilise monomeric tubulin (Ramadani et al, 2001).

Other investigations on the possible mechanism of action of Chelidonii radix special liquid extract on malignant cells showed similar results, suggesting a bimodal cell death effect:

- first, apoptosis, mediated by quinidine sensitive Ca^{2+}-dependent K^{+}-channels;
- second, blister cell death, by preventing microtubule formation, thus inducing polyploidy (Liepins et al, 1996).

Finally, several experimental data have suggested that Chelidonii radix special liquid extract may have immunomodulatory and immunostimulatory effects (Liepins and Nowicky, 1992; Aschhoff B, 2003).

From these experiments it can be concluded that Chelidonii radix special liquid extract inhibits the cell cycle progression of pancreatic and other cancer cells in M-phase, by stabilising monomeric tubulin, thus being mainly an anti-tubulin drug agent.

Comment

This application for orphan designation is the third submission. Following review of the first application filed in November 2002, the COMP asked the sponsor to provide specific details about the qualitative and quantitative characterisation of the product, including the possible role of any free thio-TEPA in the claimed cytostatic effect.

In the second application, the sponsor included further information on the ongoing development work to identify the active components of the product.

In the first submission the sponsor referred to the active ingredient as "5,5',5"-[Phosphinothioylidyne-tris(imino-2,1-ethanediyl)]tris[5-methylchelidoninium] trihydroxide hexahydrochloride"; in the second submission the sponsor initially applied for the same active ingredient described as "active alkaloids of Chelidonum majus" that was subsequently revised to 'Chelidonium majus alkaloids according to DAB Treated with ThioTEPA and Hydrochloric acid'. The sponsor has been informed by the EMEA that the wording of the active ingredient is not acceptable as ThioTEPA may be misinterpreted to be an active ingredient. The sponsor's revised proposal was then "Chelidonium majus alkaloids derivate with ThioTEPA"; however, in this application the name of the substance has again changed to "Chelidonii radix special liquid extract", in order to avoid any possible confusion.

Although the Sponsor has stated that "no free Thio-TEPA or aziridine ring compounds can be detected in NSC 631570", no reference is made to spectroscopy data or other chemical methods of quality assessment to support the statement. This is relevant, since Thio-TEPA is a known and approved cytotoxic drug, even if the sponsor claims that total dissociation of Thio-TEPA from chelidonine would still yield a quantity of Thio-TEPA much lower than an effective therapeutic dose.

The greater celandine (Chelidonium majus) is a yellow-flowering poppy, native to Europe and the Mediterranean basin (Class: Magnoliopsida; Family: Papaveraceae). It is also widespread in North America, having been brought there by settlers as a herbal remedy for skin problems such as warts as early as 1672. The whole plant is toxic, containing a range of alkaloids, such as Chelerythrine and chelidonine; it may also cause contact dermatitis, particularly the latex. The greater celandine is the only species in the genus Chelidonium, and is not closely related to the lesser celandine, which is in a different family.

The sponsor plans to apply for marketing authorisation in 2007.

4. Present stage in drug development

An Investigator's Brochure (004a, March 2007) was added to the application after an email request from the EMEA coordinator.

Since its first therapeutic use in 1978, NSC 631570 (administered either as neoadjuvant treatment before surgery or as combination therapy or alone) has been the subject of numerous experimental and clinical tests.

Toxicological and pharmacological development

In vitro activity against cancer cell lines:

- In vitro tests by the National Cancer Institute (NCI), Bethesda, USA, demonstrated cytotoxic activity of NSC-631570 against all of the 8 colon cancer cell lines tested (pancreatic cell lines were not part of this test program) at concentrations between ≈7.6 µg/mL and 76.0 µg/mL. The experiments also show that the activity profile of NSC-631570 is clearly different from the profile of its basic components thiotepa and chelidonine hydrochloride, both less active in the majority of the 53 cell lines tested.
- In a series of experiments with 14 different cell lines of human and animal origin, including normal and cancer cell lines, the effects of 4 different doses of NSC-631570 (0.1, 1.0, 10, and 100 mcg/ml) on DNA, RNA and protein synthesis were investigated by measuring the incorporation of 3-H labelled thymidine, uridine and leucine (Nowicky et al, 1996). Usually, a dose-dependent inhibition of all anabolic processes, DNA, RNA and protein synthesis was found that was more pronounced in malignant cells than in normal cells, even in those normal cell lines known for fast replication rates.
- In vitro effects of NSC-631570 on four human Ewing sarcoma (EWS) cell lines were studied and compared with the cytotoxicity of thiotepa, Chelidonium majus alkaloids, doxorubicin, cyclophosphamide and etoposide. The effects of NSC-631570 were superior to that of thiotepa and comparable to that of etoposide, which has been proven effective in the treatment of EWS. NSC-631570 was inferior to doxorubicin and the activated form of cyclophosphamide, which belong to the most active drugs in the treatment of EWS.

- The concentration of NSC 631570 which is toxic for healthy cells is more than 100 times higher than the concentration lethal for all cancer cell lines. Its therapeutic index is 1250 (Nowicky et al, 1996; Nowicky et al, 1996; Panzer et al, 1998; Roublevskaia et al, 2000; Cordes et al, 2002).

Procedure for the determination of the biological activity

Experiments and procedures were performed to 1) characterise the effects of NSC-631570 on pancreatic cancer cells, and 2) develop a routine test procedure to ensure comparable biological activity in each new batch of NSC-631570. The stability and similarity of biological activity of all tested NSC-631570 batches was confirmed.

In vivo activity

In the study by Sotomayor et al. (University of Miami School of Medicine, Miami, Florida, USA, 1992) various doses of NSC 631570 and various routes of administration (intravenous, intraperitoneal, subcutaneous) were tested in mice. The optimal administration route was judged to be intravenous and the optimal dose inducing the best remission was estimated to be 4 mcg per mouse. This dose corresponds to a human single dose of about 7-10 mg for 70 kg body weight.

Toxicity

NSC-631570 demonstrated a low acute toxicity. The LD50 in rats after i.v. application is 43 and 76mg/kg b.w. (males and females respectively), in mice 80 and 68 mg/kg b.w. (unpublished report of the Austrian Research Centre, Seibersdorf, Internal study code A-4483, Oct. 1998 and L-0400, May 2000). This is at least 300 times above the usual therapeutic dose in man.

In a 6-month i.v. toxicity study with rabbits (0-negative control, 0 -negative control recovery, 0.07 - low dose, 0.30 -mid dose, 0.70 -high dose and 0.70 mg NSC 631570 /kg -high dose recovery, groups of 6 animals each), statistically significant differences between dosed groups and the control group were observed with regard to bone marrow and the kidneys. Differences also occurred in white blood cells, with a slight increase of leukocytes, lymphocytes and bands in the high dose group (both sexes) after 4 months. Haematocrit and reticulocytes were also slightly increased in the high dose group. Occasionally, other differences between the groups were observed but can be considered as not medically relevant (Austrian Research Centre Seibersdorf, 2001).

In more than 20 clinical studies performed with NSC 631570 no signs of toxic effects on the liver were found; on the contrary, the compound can be successfully used to protect the liver from toxic damages in the acetaminophen-induced hepatitis model in rats (Levina et al, 2004).

The Sponsor concludes that administration of NSC 631570, contrary to thiotepa and alkaloids in similar doses, has no hepatotoxic activity. Also, the previously findings that the drug possesses other pharmacological properties compared with the start components for its synthesis seem confirmed.

Pharmacokinetics

Animal experiments suggest that NSC-631570 concentrations are highest in tumour tissues (2.84-fold higher than in plasma), followed by normal liver and kidney tissues; the lowest concentration was found in muscles and the brain. NSC-631570 does not significantly cross the blood-brain barrier (Doroshenko et al, 2000).

Clinical development

Several clinical studies with NSC-631570 have been carried out in non pancreatic cancer; one of them was carried out to estimate the optimal clinical dosage of NSC 631570 and included 70 advanced stage cancer patients. The patients' general condition improved in most cases, with normalisation of appetite and improvement of quality of life. Tumour regression was seen in some cases as encapsulation which made surgery possible. Positive results were clearly observed in patients whose tumours were not too extensive. The study failed to estimate a single optimal dose of NSC 631570, but the most beneficial were doses of 5, 10, 15 or 20 mg per injection every or every second or every third day.

Pharmacokinetics

In a pilot study, NSC 631570 was administered to 6 healthy men at a dose of 20 mg / 20 ml, undiluted, as a slow intravenous injection; plasma concentration was determined 5, 15, 30, 45, 60, 90, 120, 150, and 180 min after administration, urine was collected over 24 hours. In this study the half

life of NSC-631570, t1/2 beta was 27.55±2.45 minutes and the apparent volume of distribution was 27.93 ±.38 l. Around 47% of NSC-631570 was found in the urine, more than half of the amount being eliminated during the first 6 hours (Uglianica, 1999). No significant changes with regard to results of physical examination, laboratory parameters and ECG were reported.

Binding to human plasma proteins seems to be insignificant at around 2% (Doroshenko et al., 2000).

Histological features of pancreatic ductal adenocarcinoma after NSC 631570 administration

Susak (2003) performed a study to define histological features of pancreatic ductal adenocarcinoma after NSC 631570 administration. Six non-smoking, male, 57±5 years old, patients with histological verified pancreatic ductal adenocarcinoma. All the patients had previously received palliative surgical treatment with subsequent chemotherapy with gemcitabine or 5-fluoruracil. All the patients then received 2±1 courses NSC 631570 (30 mg weekly, 120 mg per course). The last injection of NSC 631570 was performed 10-12 hours before the operation. Necrosis areas squares were increased by 50-70% compared with existing previous (before NSC 631570 administration) stains.

Clinical development in pancreatic cancer

- 90 patients with histologically proven unresectable pancreatic cancer were included in a monocentric, controlled, randomised study at the University of Ulm, Germany. Patients in arm A received 1000 mg gemcitabine/m2, those in arm B received 20 mg NSC 631570, and those in arm C received 1000 mg gemcitabine/m2 followed by 20 mg NSC 631570 weekly. Actuarial survival rates after 6 months were 26%, 65% and 74% in arms A, B and C, respectively. The authors concluded that in unresectable advanced pancreatic cancer, NSC 631570 alone and in combination with gemcitabine nearly doubled median survival times (Gansauge et al, 2002).
- A study by Zemskov et al. in Ukraine included 42 patients with pathologically diagnosed pancreatic cancer. Patients were randomly assigned to treatment with vitamin C plus NSC 631570 or vitamin C plus normal saline. The NSC 631570 therapy cycle was 10 mg intravenously, every other day, up to 100 mg. One-year survival was 76% in the NSC 631570 group and 9.5% in the control group; 2-year survival was 48% in the NSC 631570 group and 5% in the control group (Zemskov et al, 2002).
- In an open study (Aschhoff, 2003), 28 patients are described with a prolongation of the mean survival to 26.13 months after starting treatment with NSC 631570 (27.97 months after diagnosing of inoperable pancreatic adenocarcinoma respectively).
- In an adjuvant study, 30 patients were treated with NSC 631570 and gemcitabine after pancreatic cancer resection. The median survival according to Kaplan-Meier regression analysis was 33.8 months (Gansauge et al, accepted for publication in Hepato-Gastroenterology, 2007).

The Sponsor believes that the relatively important differences in survival reported in these four studies (8.1 m – 18.8 m – 26.1 m – 33.8) may be explained by differences in the population, and also of the dosage: patients of the study of Zemskov et al. had a slightly better prognosis (only 71.4% were of UICC Stage 4a or 4b compared to 96.7% of the German study). In addition, none of the Ukrainian patients had a previous chemo- or radiotherapy in contrast to 2 of the German patients. Finally, the weekly dose and treatment duration (total dose) was slightly different.

A systematic review on randomized clinical trials with NSC 631570 has been published in 2005. The authors conclude that "data from randomized clinical trials suggest that NSC 631570 has potential as an anticancer drug. However, numerous caveats prevent a positive conclusion, and independent rigorous studies are urgently needed" (Ernst, Schmidt, 2005).

Comment

The Sponsor sent the Investigator's Brochure after being requested via email.

The data in this application are the same as in the previous two applications, with the exception of the last study (30 patients) by Gansauge et al., to be published in Hepato-Gastroenterology (accepted 4 Oct 2006).

The clinical data in pancreatic cancer come from 4 published studies. All of these present methodological and practical issues that severely impair their usefulness, when evaluating the medical plausibility and particularly when examining the claim of significant benefit. The most important problems are reported below.

The study by Zemskov et al. (2002) does not specify the statistical methods employed for the analysis; indeed, no statistical comparison was performed between the two groups, there being only descriptive results. Histology is also not well described. There is confusion on the objectives: although the authors claim in the introduction that they intended to evaluate Ukrain "in controlling the growth of pancreatic cancer, and improving the quality of life", in the abstract and in the results much more prominence is given to survival data. There is no clear definition of the primary endpoint, sample size calculation, and estimation of the expected effect of the drug. Although the Authors state that they intended to evaluate patients "in the late stages of this disease where prognosis is extremely poor", the studied group included patients with very different stages, from II to IV. Also, although this study is placebo-controlled, only patients who refused chemotherapy were enrolled, and where then given a choice between placebo and an active treatment (Ukrain); this is likely to introduce selection bias and undermine the external validity of the results.

The inclusion criteria in the Gansauge et al. (2002) study are unclear; in particular, the staging criteria of the patients before inclusion are not specified, and similarly whether endoscopy was performed on all patients, whether there was pre-treatment blinding, etc. No statistical methods are cited in the article, regarding randomisation or analysis of the data. There is no power estimation or sample size calculation, and the primary endpoint is unclear. Also, there seems to be bias introduced during the study, as response was evaluated only in patients who had an increased Ca19.9 level or who were alive at the time of re-evaluation. Patients in Arm A (gemcitabine only) received less treatment cycles than those in arm B (Ukrain) and arm C (Gemcitabine + Ukrain), and for arm C this difference is statistically significant; the authors do not discuss this discrepancy, which can profoundly affect the results of the clinical trial. Finally, in the Ukrain only group, almost one third of patients had been treated for less than 3 months at the time of the evaluation of results, which renders the survival data unreliable.

The study by Aschoff (2003) is a retrospective study. The inclusion and allocation criteria are not specified, so bias cannot be excluded. The staging of the disease before and after treatment is not specified, and neither are the evaluation criteria (WHO? RECIST? others?). Also, criteria for evaluating toxicity are not specified.

The Gansauge et al. (2007, in press) study, which is an adjuvant trial in operable patients, is a single-arm case series study (with Gemcitabine plus Ukrain), and moreover there is a lack of a placebo group (which would have been necessary since there is no authorised drug for the adjuvant therapy of pancreatic cancer). Thus it is not possible to discriminate the effect of Ukrain from that of gemcitabine, or to establish if any effect of the treatment is present at all, as the only comparison is with historical data. It must be added that all patients in this study had tumour-free resection margins at surgery, and thus constituted a highly preselected group with a better prognosis in the first place.

Prof. Hans Winkler (EMEA/COMP expert) also expressed concern about the reproducibility of the clinical data, due to several methodological issues:

Regarding the Aschhoff et al. study (2003), the results can not be evaluated, e. g. there were no control groups and there is no methodical description how tumour shrinkage was determined. The Gansauge et al. (2002) study has been severely criticised by the German Medical Association (Arzneiverordnung in der Praxis-Ausgabe 2/2002, p.9); the study was not blinded, therefore results on quality of life and tumour regression are not reliable. Furthermore, for the tumour marker response (Ca19.9), no significant differences between the three groups were observed. Also, randomisation apparently did not work well, since there were difference among the groups for sex and age: particularly worrying was the fact that the Ukrain groups included younger patients (lowest age: 22 year and 40 versus 53 in the gemcitabine group). Patients in the Ukrain group also had a history of more chemotherapy and radiochemotherapy. For all these reasons, the differences seen in survival time may be explained by methodical irregularities.

In the study by Zemskov et al. (2000), randomisation apparently did not yield comparable groups, since men represented 81% in the Ukrain and only 47.6% in the control group; but on the other hand, which appears surprising, all the clinical parameters seemed to match extremely well for such small groups of patients. The survival rates of the Zemskov study showed remarkable results: in the control group more than 90% of patients had died within one year, compared to 24% in the Ukrain group; however, no further data concerning tumour growth, development of metastases etc, were presented. As data presented in a Journal are necessarily limited, it seems essential to obtain the original study protocol to evaluate this study. Finally, for the (as yet unpublished) Gansauge et al. (2007) study, the absence of a control group and the small size of the investigated group makes it difficult to reach a reliable conclusion.

III CRITERIA FOR ORPHAN DESIGNATION

1. Prevalence of the condition

Medical plausibility

Sponsor's position

According to the sponsor, preclinical experiments indicate that Chelidonii radix special liquid extract inhibits the cell cycle progression of pancreatic and other cancer cells in M-phase by stabilising monomeric tubulin (Ramadani et al, 2001), thus being an anti-tubulin drug agent. In addition, it might inhibit (reversibly) angiogenesis (Koshelnick *et al*, 1998), and induce apoptosis (Roublevskaia et al, 2000).

Three clinical studies in patients with pancreatic cancer were performed and reported in a peer-reviewed journal, and a fourth one has been accepted for publication in 2007. In the first three studies therapy was well tolerated and no severe side effects occurred. In no cases was it necessary to stop therapy due to side effects.

The highest weekly dose (60 mg) combined with a high extent of exposure (min. 720 mg/3 months) produced the highest survival rate of pancreatic carcinoma patients despite of a poor prognosis: 21 of 28 patients had been unsuccessfully treated with chemotherapeutics before receiving that Chelidonii radix special liquid extract (Aschhoff, 2003).

Comment

Concerning the rationale for the development of Chelidonii radix special liquid extract (Ukrain) in pancreatic cancer, this is mostly based on a preclinical observation of cytotoxic activity. Comparative pharmacodynamic studies in vitro and/or in vivo with the current authorised treatments of pancreatic cancer are lacking. Also data on resistant cell lines are missing. Furthermore, the selective cytotoxicity of Ukrain for cancer cells has been questioned in at least one published study from an independent group (Panzer A et al., 2000).

Prof. Hans Winkler (EMEA/COMP Expert) also expressed doubts on the claimed greater cytotoxicity of Ukrain for cancer cells than for normal cells, based on the reported study by Panzer A et al. (2000), thus finding difficult to accept the Sponsor's claim that the concentration at which toxic effects are seen in healthy cells is more than 100 times higher than that lethal for all cancer cell lines.

Four clinical studies were done in altogether 190 patients diagnosed with pancreatic cancer, claiming a substantial effect on survival for patients treated with Ukrain. However, the two allegedly randomised studies had multiple imbalance issues, which seriously impair the possibility of a clear interpretation of the results. The lack of the full protocol and results, repeatedly requested by EMEA to the Sponsor in this and in previous occasions but not provided, prevents an objective evaluation of the results. The two other studies, as reported in the previous comment, also present multiple methodological problems.

Indeed, the four reports showed a significantly different average survival time among them: from 8.1 to 33.8 months. This is acknowledged by the Sponsor, who attributes it to "differences in the population and the dosage employed", but could easily be attributable to some of the methodological faults that have been discussed, rather than to the effect of the treatment.

A recent independent review in a peer-reviewed journal, on the potential effectiveness of Ukrain in oncology concluded that "the methodological quality of most [Ukrain] studies was poor. In addition, the interpretation of several trials was impeded by other problems". Also, the Authors stated that: "numerous caveats prevent a positive conclusion, and independent rigorous studies are urgently needed" (Ernst and Schmidt, 2005).

To date, these independent studies are not present in the literature. Indeed, when other researchers tried to investigate Ukrain in a phase II clinical trial, to establish its effectiveness in several forms of cancers, they reported to have been unable to obtain the drug (Farrugia and Slevin, 2000).

The published literature on Ukrain in preclinical and clinical conditions is considerable; however it is of interest that, of 159 articles found on PubMed with the keyword "Ukrain", more than three quarters of them (121/159, or 76.1%) were published in a single scientific journal (Drugs under experimental and clinical research, Impact Factor 1.15 [ISI 2005]).

In conclusion, the pharmacological rationale for the development of Chelidonii radix special liquid extract for the treatment of the condition is not clearly established at present, and major methodological flaws have been highlighted in the clinical studies performed. These facts make it difficult for the COMP to draw a conclusion on the activity of the product in the proposed condition.

Prevalence

Sponsor's position

The Sponsor , by summarising statistical data, estimated that the prevalence of pancreatic carcinoma in the European Community is about 1.1 in 10,000.

The incidence of pancreatic carcinoma has increased in Northern Europe and North America during recent decades and contrary to for example, lung, gastric and oesophageal carcinoma, its incidence is still increasing. Annual incidence is about 8-10/100,000 of the population. (Eskelinen et al, 1999)

According to EUCAN database published by European Network of Cancer Registries (ENCR), and 'Globocan 2002: Cancer Incidence, Mortality and Prevalence Worldwide', the incidence of pancreatic carcinoma in the European Union, Iceland, Liechtenstein and Norway (EU25+3) was estimated as 56,676 cases, 1-year prevalence as 13,567 cases, and 5-year prevalence as 29,276 cases.

Country	Population*	Incident cases	1-year prevalence cases	5-year prevalence caces	Incidence
Austria	8,206,500	1,239	236	678	1.51
Belgium	10,445,900	965	257	666	0.92
Bulgaria	7,761,000	821	160	370	1.06
Cyprus	749,200	70	19**	44**	0.93
Czech Republic	10,220,600	1,534	303	728	1.50
Denmark	5,411,400	722	117	221	1.33
Estonia	1,347,500	184	37	97	1.37
Finland	5,236,600	691	163	292	1.32
France	62,518,600	5,321	1,761	3,605	0.85
Germany	82,500,800	10,334	2,738	5,933	1.25
Greece	11,082,800	1,211	309	657	1.09
Hungary	10,097,500	1,597	308	707	1.58
Iceland	293,600	19	4	9	0.65
Ireland	4,109,200	332	69	138	0.81
Italy	58,462,400	8,602	2,341	4,814	1.47
Latvia	2,306,400	347	74	152	1.50
Liechtenstein	34,600	4	1**	2**	1.16
Lithuania	3,425,300	391	82	168	1.14
Luxembourg	455,000	45	12	26	0.99
Malta	402,700	44	13	33	1.09
Netherlands	16,305,500	1,491	387	759	0.91
Norway	4,606,400	557	123	222	1.21
Poland	38,173,800	4,357	826	1,730	1.14
Portugal	10,529,300	874	221	471	0.83
Romania	21,658,500	2,049	398	921	0.95
Slovenia	1,997,600	246	49	90	1.23
Slovakia	5,384,800	615	117	288	1.14
Spain	43,038,000	3,879	843	2,016	0.90
Sweden	9,011,400	910	199	367	1.01
United Kingdom	60,059,900	7,225	1,400	3,072	1.20
Total, EU27+3* **	**495,832,800**	**56,676**	**13,567**	**29,276**	**1.14**

*As of January 1, 2005. Source: Lanzieri, 2006.

**Own estimation.

*** 27 member countries of European Union + Iceland, Liechtenstein, and Norway

Table 1: Population, incidence and prevalence of pancreatic carcinoma in the European Union, Iceland, Liechtenstein, and Norway.
Sources: Eurostat, EUCAN version 5.0, created 17-03-2003, and Globocan 2002

Comment

Pancreatic cancer has been designated as an orphan condition 12 times by the EU Commission. The sponsor has provided a detailed and well-discussed report of the available data on the incidence/prevalence of the condition.

Given the given the high aggressiveness of pancreatic cancer, most new cases result in patient death within the same year. As a result, the "deaths to new cases" or DNC ratio is over 90%, and median survival time is approximately 4-6 months. For these reasons, incidence can be used to estimate the prevalence of the disease.

In conclusion, the sponsor has established that the number of persons affected by the condition in the Community when the application was made is less than 5 in 10000, and is estimated to be about 1.1 / 10,000.

2. Seriousness of the condition

Sponsor's position

Pancreatic cancer causes late symptoms, and diagnosis is therefore late and cure rare. At the time of diagnosis most patients show progression of the disease beyond the pancreas, either through the direct invasion of neighboring structures or metastases in regional lymph nodes, liver, peritoneum, lungs, bones, or brain. Therefore, up to 90% of patients present with incurable, advanced disease (Dowsett and Russell, 1995).

Median survival time is approximately 4-6 months after diagnosis. Fewer than 10% of patients survive 1 year after diagnosis, and many suffer from increasingly severe pain, nausea and vomiting, anorexia, weight loss, and weakness as the disease progresses. The overall European mean 1 year relative survival rate is 15% for pancreatic cancer (Faivre *et al*, 1998). The 5-year survival for pancreatic cancer is usually less than 5% and has not changed during the past 30 years (Crino *et al*, 2001; Philip *et al*, 2001; Faivre *et al*, 1998).

Comment

The sponsor has provided satisfactory argumentation to establish that the condition is life threatening, in particular due to a very poor overall survival.

3. Currently available methods for diagnosis, prevention or treatment of the condition

Sponsor's position

Pancreatic cancer remains one of the most difficult cancers to treat at the present time. In the few cases in which early diagnosis is made, surgical pancreatico-duodenectomy may be attempted by those with skill and experience in performing this challenging operation. Currently resection rates of up to 14% (Wade et al, 1996) and operative mortality rates of less than 5% to 10% are being achieved. Some studies showed better results in patients treated with postoperative radiotherapy (Dobelbower et al, 1997), but the presence of critical radiosensitive organs such as the liver, kidneys and small intestine limits the dose that can be delivered to this site (Morganti et al, 2002). The methods which enable the intensification of radiation treatment such as intraoperative radiation therapy and concomitant chemoradiation (Yeo et al, 1997) can improve treatment results of resectable carcinomas.

The standard systemic treatment for advanced pancreatic cancer was 5-fluorouracil (Morrell et al, 1991). The drug acts as a pyrimidine antimetabolite (Peters et al, 1996). The addition of modulators to 5-FU such as folinic acid, hydroxyurea, or interferon-alpha did not produce substantial improvements in response rates and led to significant toxicity even in highly selected patients with an ambulatory performance status (Wadler et al, 1999; David et al, 2000). One of the better alternatives to 5-FU is gemcitabine, a deoxycytidine analog that became the standard first-line therapy for patients with advanced pancreatic carcinoma (Burris et al, 1997). The drug acts by intracellular activation into phosphorylated metabolites: one of them competes with endogens deoxycitidine triphosphate for incorporation into DNA, the other one inhibits ribonucleotide reductase. Three biochemical mechanisms underlie the so-called self potentiation process of gemcitabine activity: inhibition of ribonucleotide reductase, stimulation of deoxycitidine kinase and inhibition of deoxycitidine monophosphate deaminase (Peters et al, 1996). Gemcitabine monotherapy resulted in a median survival of 5.6 (Berlin et al, 2002), 7.3 (Crino et al, 2001) and 8.8 (Ulrich-Pur et al, 2000) months.

Comment

Gemcitabine is authorised for the condition in the European Community. 5-fluorouracil and mitomycin are authorised for the treatment of gastrointestinal tumours, including pancreatic cancer. Erlotinib (Tarceva™) was authorised, via centralised procedure, by the EU Commission for metastatic pancreatic cancer on 24 January 2007.

Besides chemotherapy, surgical resection and radiotherapy are used for curative treatment and mainly for palliative treatment.

4. Significant benefit

Sponsor's position

The mechanism of action of NSC 631570 (Ukrain, or Chelidonii radix special liquid extract) differs from that of gemcitabine, 5-FU, epirubicin, cisplatin and taxanes – it is an inhibitor of tubulin polymerization in G2/M phase. In contrast to taxol and other taxanes (which also act as tubulin inhibitors, but in phase M) NSC 631570 prevents the formation of mitotic spindles in the G2/M phase of the cell cycle, whereas taxol acts as a inhibitor of existing mitotic spindles in the M phase.

The combination of NSC 631570 (which is an inhibitor of tubulin-polymerization in G2/M phase and prevents mitotic spindle formation) and gemcitabine (which acts as a pyrimidine antagonist-antimetabolite) should be more effective against cancer cells because of it uses two different mechanisms of action against malignant cells and one of the drugs (NSC 631570) has no toxic effects and seems to have immune modulating action (Zemskov et al, 2002; Gansauge et al, 2002).

Also, NSC 631570 accumulates selectively in cancer cells (Nowicky et al, 1996), and could be used combined with radiotherapy because it protects human non-malignant but not human tumour cells in vitro against ionising radiation (Cordes et al, 2002).

Finally, several experimental data have suggested that Chelidonii radix special liquid extract may have immunomodulatory and immunostimulatory effects (Liepins and Nowicky, 1992; Aschhoff B, 2003).

Aschhoff (2003) reported on palliative therapy with Chelidonii radix special liquid extract (Ukrain) (total first three-month dose 720 mg, and then next four-month dose 320 mg) of 28 patients with unresectable pancreatic adenocarcinoma. Twenty-one patients had previously been treated with conventional chemotherapy modalities, however, this therapy had failed and disease progressed. Of the 28 patients treated with Ukrain, partial remission was achieved in 24 cases (85.7%) while four patients did not respond to treatment. The mean survival of the patients treated with Ukrain was 26.1 months after the start of Ukrain administration and 28.0 months after the diagnosis of inoperable pancreatic adenocarcinoma.

In the report on the treatment with Ukrain and gemcitabine of four advanced pancreatic cancer cases (Gansauge, 2003) the author noted partial remission and the reduced toxicity profile of the drug. The findings were especially surprising because all the patients had exhausted traditional methods of therapy before Ukrain therapy, and surgical treatment was also impossible.

In the Gansauge et al. (2002) study, Ukrain alone or in association with gemcitabine was significantly better than gemcitabine alone (median survival 8.1, 9.3 and 4.8 months respectively).

Comment

Comparative pharmacodynamic studies in vitro and/or in vivo with the current authorised treatments of pancreatic cancer are not described in the sponsor's application.

The Gansauge et al. (2002) comparative study with gemcitabine showed an improved overall survival after Chelidonii radix special liquid extract treatment or coadministration. This study however suffers from methodological issues, which impair the value of the study itself as the basis for a claim of significant benefit, as explained in the comments on the clinical development of the product (see comments in section II.4).

Tarceva (erlotinib) has been authorised by the EMEA for the treatment of pancreatic cancer before the Sponsor submitted its application. The Sponsor did not initially submit a claim of significant benefit over erlotinib.

Given the lack of preclinical comparative data, and the multiple methodological issues of the single clinical comparative study performed with the use of currently authorised products, it is difficult to accept the claim of significant benefit over the currently authorised products.

The Sponsor was asked to provide, in writing and at an oral presentation, answers to the following questions:

1) In order for the COMP to fully and scientifically evaluate the claim of significant benefit, the Sponsor is requested to provide, for the four published clinical studies, the complete original study protocols, in addition with the full study reports (elaborated according to ICH guidelines, as published on http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf.

2) As described in the draft guideline on significant benefit, available online at http://www.emea.europa.eu/pdfs/human/comp/6697204en.pdf, the Sponsor should provide justifications for the assumption of significant benefit over all currently authorized drugs. Since erlotinib (Tarceva) has been authorised for the treatment of the condition before the Sponsor submitted its application for orphan designation, the sponsor is requested to submit a discussion on the assumptions of significant benefit for Ukrain over erlotinib.

Sponsor's position on the list of questions:

In answer to the request for the complete, original study protocols and full study reports, the Sponsor stated that *"All studies so far have been investigator-initiated (non-commercial) studies. This means that the studies have been performed under the sole responsibility of the investigators, in line with national regulations."... " To our understanding, neither the availability of protocols and ICH-reports is a must at this stage of application for orphan drug status, nor data of a direct comparison between Ukrain and Erlotinib."*

The Sponsor provided a discussion of the assumption of significant benefit over erlotinib, using a comparison between the two studies with Ukrain alone or in combination with gemcitabine, and the studies with erlotinib alone or in combination with gemcitabine, concluding that although the number of patients is superior in the erlotinib studies (N=261), the combination of Ukrain and gemcitabine (N=60) is superior in terms of survival and tolerance.

Comment

The claim of significant benefit over the currently available treatment methods, in particular over gemcitabine and over erlotinib is not sufficiently supported by the currently available evidence, given the conflicting preclinical evidence, the methodological issues, and the lack of reproducibility that have been reported in the literature and commented in the previous sections.

Given the doubts about the interpretation of the published data, the COMP had requested the complete, original study protocols and full study reports, to be able to assess the data generated, in the context of the justifications for the assumption of significant benefit.

The Sponsor has not submitted the complete, original study protocols and full study reports, as requested, citing the fact that the four clinical studies, on which the claims for significant benefit are based, were investigator-originated and not the property of the Sponsor. Consequently, the EMEA contacted the four corresponding Authors of the clinical articles, requesting further information on the methods and the results. Dr. Gansauge answered by resubmitting information already contained in the draft manuscript accepted by Hepato-Gastroenterology (2007). Dr. Prokopchuk stated that the complete data are in the Ukraine hospital where she worked at the time of the study, and would contact colleagues there, in order to provide the required information; at the time of the second COMP meeting (30-31 May 2007) this information had not arrived at the EMEA.

Finally, although the Sponsor is correct in stating that submission of these data is not compulsory at the stage of orphan designation, accepting the claim of significant benefit based only on the data published in the literature is difficult, given the multiple methodological problems of these articles, as already outlined.

The EMEA/COMP Expert Prof. Winkler expressed doubts regarding the claim of improved safety reported by the Sponsor:

A hepatotoxic effect of these alkoloids has been established. Benninger et al. (Gastroenterol. 117, 1234, 1999, see also Deutsche Apothekerzeitung 142, 32 2002) reported 10 cases of cholestatic hepatitis. Panzer et al. (Cancer letters 150, 85, 2000 c) state and quote literature: "Chelidonine has long been found to have side-effects, in doses which are tumorolytic, too severe to justify its use in clinical medicine."

The claim by the company for Ukrain that is has little side effects, and no hepatotoxicity, is therefore difficult to accept.

In the Investigator's Brochure a 6 month study on rats (i.m.) is presented. In this study "a minimal to mild hepatocellular degeneration at all doses" was reported. As an explanation for the claim of a low toxicity of Ukrain Panzer et al. (2000) suggest: "The lack of side-effects found in vivo may be due to the lack of therapeutically effective dosages being administered".

In conclusion, the Sponsor has not supplied sufficient argumentation to claim a potential significant benefit of Chelidonii radix special liquid extract over currently authorised treatments for treatment of pancreatic cancer, neither through better efficacy, better safety, or a significant contribution to patient care.

5. Demonstration of insufficient return on investments

Not applicable.

6. Overall conclusions

Pancreatic cancer is a distinct medical entity and thus a valid condition. However, the scientific rationale for the development of Chelidonii radix special liquid extract for the treatment of the condition is not clearly established.

The sponsor has established that the condition was affecting approximately 1.1 in 10 000 persons in the Community when the application was made.

The sponsor has established that the condition is life threatening due to a very poor overall survival.

The sponsor has established that, despite existing authorised methods of treatment there remains an important need for improving existing treatments or improving the overall outcome of patients affected by the condition.

However, based on the pre-clinical evidence, the preliminary clinical data, the justifications provided, the opinion of the COMP experts, and the published literature, the assumption that Chelidonii radix special liquid extract could be of potential significant benefit for patients affected by the condition does not appear justified.

IV GROUNDS FOR THE OPINION ON ORPHAN MEDICINAL PRODUCT DESIGNATION

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- Pancreatic cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening due to a very poor overall survival;
- satisfactory methods of treatment of the condition have been authorised in the Community, and the sponsor has not provided sufficient justifications that chelidonii radix special liquid extract may be of significant benefit to those affected by the condition, over currently authorised treatments for pancreatic cancer, neither through better efficacy, better safety, or a significant contribution to patient care.

The Committee for Orphan Medicinal Products has recommended the refusal of the granting of the designation of chelidonii radix special liquid extract as an orphan medicinal product for treatment of pancreatic cancer.