13 July 2016
EMA/COMP/399656/2016 **CONFIDENTIAL**
Committee for Orphan Medicinal Products

EMA/COMP summary report

On an application for orphan medicinal product designation

Cisplatin

Treatment of malignant mesothelioma

EMA/OD/101/16

Sponsor: PlumeStars s.r.l.

This report represents a critical review of the application for orphan medicinal product designation. It assesses whether the sponsor has established that the criteria for designation provisioned in Article 3 of Regulation (EC) No 141/2000 are met.
For the full details of the data evaluated by the COMP, please refer to the sponsor's application included in the supporting documents below.

Supporting documents

- Sponsor's application

2. Hyalcis Scientific Section A-E .docx

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Contents

1. Product and administrative information 3

2. Criteria for orphan designation..... 4

Article 3 (1)(a) of Regulation (EC) No 141/2000 4

Article 3(1)(b) of Regulation (EC) No 141/2000 7

3. COMP list of issues 8

4. Grounds for the opinion on orphan medicinal product designation..... 9

1. Product and administrative information

Product	
Active substance:	Cisplatin
International Non-proprietary Name (INN), (accompanied by its salt or hydrate form if relevant):	Cisplatin
Proposed invented name of the medicinal product (tradename):	Hyalcis
Orphan indication:	Treatment of malignant mesothelioma
Pharmaceutical form:	Implant
Route of administration:	Intrapleural use
Sponsor:	PlumeStars s.r.l. Strada Inzani 1 43125 Parma Italy
Procedural history	
COMP Co-ordinator:	D. O'Connor / B. Dembowska
EMA Co-ordinator:	S. Mariz
Expert:	No experts were appointed by the COMP for this application
A pre-submission meeting was held on	28 April 2016
The sponsor submitted the application on	23 May 2016
The procedure started on	13 June 2016
Circulation of draft summary report to COMP on	28 June 2016
The application was discussed by the COMP on	11-13 July 2016

- During the meeting on 13 July 2016 the COMP, in the light of the overall data submitted and the discussion within the Committee, issued a positive opinion by consensus on orphan medicinal product designation for cisplatin for treatment of malignant mesothelioma on 13 July 2016.

Regulatory considerations

- The COMP recommends that protocol assistance is sought from the Agency prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit
- Due to the potential interest of developing the product in a paediatric indication in the proposed condition and in related conditions where the medicinal product could be used, the sponsor is advised to (i) consider the requirements of Regulation (EC) No 1901/2006 with regards to the development and application for marketing authorisation of the medicinal product, and (ii) consider the possibility to apply for orphan designation for those conditions affecting children and where a paediatric development can be requested.
- It should be highlighted that further to Article 5(12)(b) of Regulation (EC) No 141/2000 and Article B 2.1 of Communication from the Commission on Regulation (EC) No 141/2000, when a sponsor submits an application for marketing authorisation for a designated orphan medicinal product, it is

the responsibility of the sponsor to submit a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria.

2. Criteria for orphan designation

Article 3 (1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Mesothelioma is an aggressive cancer originating from the surface mesothelial cells of the pleural, peritoneal, and pericardial cavities.

The primary cause of malignant mesothelioma is asbestos exposure. In vitro data shows that asbestos exposure induces the epidermal growth factor, ERK and AP-1. These mechanisms would result in cell growth and transformation. Other mechanisms through activation of NFκB and DNA transcription have been also identified.

Symptoms of mesothelioma are unspecific and this causes significant delay in diagnosis, which is normally done when the cancer is in an advanced stage. This in turn leads to a poor prognosis of the disease, which is characterised by a median overall survival of 7 months without treatment. Even with treatment, malignant mesothelioma remains an aggressive and highly symptomatic cancer with short survival expectation. The median survival from the time of diagnosis is 8 – 12 months. Characteristically the condition develops complications such as respiratory failure due to incarceration of the lungs, which is the main cause of death in these patients.

Malignant mesothelioma is a valid condition which has been previously designated.

Intention to diagnose, prevent or treat

Cisplatin (or cis-diamminedichloroplatinum) is a metallic platinum coordination compound. Notwithstanding the introduction of other platinum based anticancer drugs, cisplatin has a still growing field of application and has been surpassed in efficacy only by carboplatin. As for other platinum compounds, the mechanism of action at cellular level is related to the formation of highly reactive intracellular species formed after the drug uptake into cells, able to interfere with cancer cells replication by forming platinum-DNA adducts.

Cisplatin enters cells by passive diffusion, even if recently data have highlighted a link with proteins involved with the regulation of cellular levels of copper. Once inside the cell, cisplatin undergoes aquation forming Pt[(NH3)2(OH)2]2+. The aquated form is more reactive and forms adducts with many cellular components; however, DNA is the primary target of the drug. The platinum atom forms covalent bonds to N7 position of purine bases to generate 1,2 or 1,3 intra-strand crosslinks and a lower number of inter-strand crosslinks. DNA modifications, due to cisplatin distorting, are activating a number of cellular signalling pathways that induce replication arrest, transcription inhibition, cell cycle arrest, activation of DNA-repair mechanism and ultimately cell death by necrosis or apoptosis.

The medicinal product (HA-CisPt film) proposed in this application is an implant for intrapleural application of cisplatin to be implanted during surgery for tumour resection to prevent local recurrence.

The implant is a polymeric film of hyaluronic acid loaded with cisplatin. The aim was to develop a hydrophilic, thin and flexible film sufficiently resistant to be applied intrapleural adhering to the mesothelial surface. The release of cisplatin from the film is prolonged with the intent to provide high local concentrations of the anticancer drug, precisely in situ where the residual tumour is present.

The sponsor has submitted one pre-clinical in vivo study in a rat model of the condition. A preclinical study on efficacy of HA-CisPt film was performed in rats. The primary endpoint of this study was the reduction of tumour volume due to the intrapleural HA-CisPt in a rat model of MPM. Secondary endpoints were cisplatin level in serum at different time points, toxicity of the treatment measured by the analysis of animal blood, histological examination of organs removed. A well-established orthotopic rat recurrence model of malignant pleural mesothelioma was used.

Briefly, tumour nodules of 5.5 mean diameter (ranged 4.4 mm – 6.1 mm) developed in six days after subpleural rat mesothelioma cells IL-45 inoculation (50 µl containing 1*106 cells). At day 6 after inoculation, pleural tumour resection and pneumonectomy were carried out. Thus, twenty rats (male, Fisher 344 rats, mean weight 291 g), randomly assigned to four different treatment groups prior to tumour cell inoculation, were treated according to the following scheme:

a) Control (no cisplatin therapy);

b) Blank hyaluronate (HA) film;

c) Cisplatin solution (1.5 ml NaCl 0.9% containing 0.6 mg/ml cisplatin in order to have 900 µg, i.e. 3 mg/Kg);

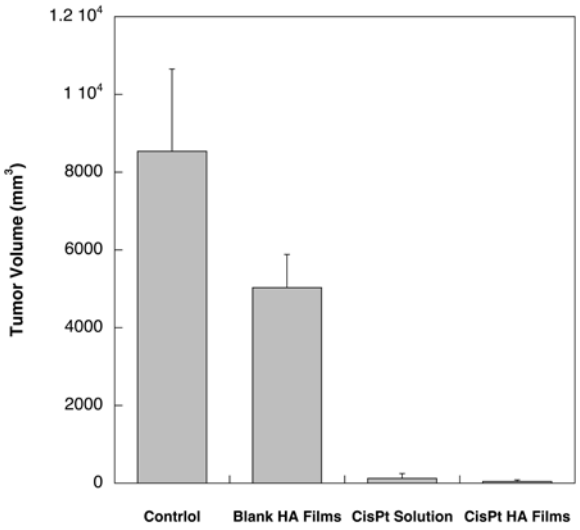
d) Cisplatin loaded hyaluronate film (HA-CisPt) 0.5% w/w; 50 µg/cm2; 4.5 cm diameter, dose 3 mg/Kg).

Six days after the surgical resection and intrapleural therapy, all the animals were humanly euthanized and necropsy was performed. Animals treated with hyaluronate cisplatin had length, width and thickness of the tumour smaller than all other groups. Specifically, tumour volume was markedly lower in animals treated with cisplatin hyaluronate films and cisplatin solution, in comparison to control groups. Cisplatin loaded hyaluronate films resulted the most effective treatment in reducing tumour recurrence, even if there was not a significant difference with the cisplatin solution. Hyaluronate films dissolved without leaving any residual.

Table 1. Tumour recurrence dimensions according to the different treatment administered

Measures (mm)	**Control**	**HA Films**	**Cisplatin Solution**	**CisPt HA films**
Length	21.7 ± 2.9	19.3 ± 5.7	5.5 ± 3.4	2.7 ± 2.1
Width	27.7 ± 2.5	23.5 ± 9.2	5.2 ± 3.1	2.5 ± 2.9
Thickness	7 ± 6.1	6.1 ± 3.1	2.1 ± 1.0	1.8 ± 1.7

Figure 1. Tumour recurrence volume in orthotopic rat mesothelioma model



A major issue in studies evaluating intracavitary therapy with cytotoxic drugs is the relatively short drug exposure of local tissues, because of eventual exudate dilution, tissue rapid absorption of drug solution and systemic distribution. In this study, the intrapleural administration of cisplatin loaded hyaluronate films resulted in prolonged plasma levels of cytotoxic drug in comparison to cisplatin solution intrapleural administered, and an efficient reduction of tumour recurrence, suggesting that the in vitro prolonged release of cisplatin is present also in vivo. The cisplatin pharmacokinetic combined to its controlled release from polymeric film, enhances the local and systemic exposure of the tumour, apparently without increasing side effects. In summary, the HA-CisPt film can be adapted to the site of application allowing bending, folding, cutting and any deformation necessary to ease covering the pleural surface in a surgical setting. The prolonged release of cisplatin in situ on pleura sustains the anticancer activity and reduces adverse effects.

The sponsor has provided sufficient evidence that the product to support the medical plausibility in condition targeted.

Chronically debilitating and/or life-threatening nature

Malignant mesothelioma is a very severely debilitating and deadly disease. Main symptoms at onset include shortness of breath, cough, and pain in the chest due to an accumulation of fluid in the pleural space (pleural effusion). When the mesothelioma affects the peritoneum, symptoms include weight loss and cachexia, abdominal swelling and pain due to ascites.

Patients with malignant mesothelioma develop local complications leading to pleural effusions, dyspnoea and malignant ascites, and the majority of patients with treated or untreated mesothelioma will die of complications of local disease. Common local invasions cause enlargement of lymph nodes, and may result in obstruction of the superior vena cava, cardiac tamponade, subcutaneous extensions, and spinal cord compression. Patients with pleural mesothelioma die because of increasing tumour bulk that gradually fills the hemithorax and eventually replaces the pleural effusion, causing progressive respiratory compromise (“incarceration” of the lungs), pneumonia, or myocardial dysfunction with arrhythmias; and/or unrelenting chest wall pain requiring narcotics, which lead to cachexia; and/or dysphagia from tumour compression of the oesophagus. In patients with peritoneal mesothelioma,

distension due to ascites, abdominal pain, and occasionally organ impairment such as bowel obstruction are observed.

Mortality rates of mesothelioma are very high with a median survival of 9 months which at the maximum can be extended to 12 months after chemotherapy. Peritoneal mesothelioma presents with a median survival of 12 months and a survival after treatment of 28 to 60 months according to the sponsor.

Number of people affected or at risk

The sponsor has conducted a literature search to establish the prevalence of the condition and proposed that the prevalence is 0.9 in 10,000 in Europe.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Several methods are used for the treatment of mesothelioma, including surgery, radiation, and chemotherapy. None of these methods can change significantly the course of the disease, and the survival rates of malignant mesothelioma remain extremely poor.

Several antineoplastic agents are commonly used for the treatment of mesothelioma, even though only one (pemetrexed, Alimta) is specifically authorised in the EU for the treatment of malignant mesothelioma (this product does not have orphan status).

ESMO has recently published guidelines on how to treat the condition (*Annals of Oncology 26 (Supplement 5): v31–v39, 2015*). Radiotherapy (RT) can be used for different indications in mesothelioma: as palliation, as preventive treatment and as part of a multimodality treatment. In general, it is not recommended that RT is administered pre- or postoperatively with large fields (hemi-thoracic RT) outside the setting of a clinical trial. Surgery is used for staging procedures or with palliative or curative intent.

Front-line chemotherapy improves survival of patients with unresectable MPM. Combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a longer survival compared with cisplatin alone in randomised phase III trials. The use of continuation or switch maintenance therapy with pemetrexed monotherapy has changed practice in the management of non-small-cell lung cancer, but is yet to be evaluated in the mesothelioma setting. There is currently no second-line standard of care.

Significant benefit

The sponsor is using a medical device which contains cisplatinum as a delivery system to target the condition more effectively. This option could help in the treatment of patients with pleural forma of the condition where accessibility of the treatment could offer a more effective treatment modality to those already in existence. As the condition involves surgical intervention as a method both to assist in the establishment of the severity of the condition and as a treatment the sponsor has provided preliminary pre-clinical in vivo data which would support the use of the product in a specific setting which is not treated effectively. The product can be adapted to the site of application allowing bending, folding,

cutting and any deformation necessary to ease covering the pleural surface in a surgical setting. The prolonged release of cisplatin in situ on pleura sustains the anticancer activity and reduces adverse effects. This would be localised unresectable pleural forms of the condition which could be effectively treated with this product.

3. COMP list of issues

Not applicable.

4. Grounds for the opinion on orphan medicinal product designation

The sponsor PlumeStars s.r.l. submitted on 23 May 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing cisplatin for treatment of malignant mesothelioma (hereinafter referred to as “the condition”). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing cisplatin was considered justified based on a pre-clinical in vivo model of the condition showing a reduction in tumour nodules;
- the condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise (“incarceration” of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed;
- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cisplatin will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in pleural tumour nodules which may translate into improved management of local residual disease. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing cisplatin as an orphan medicinal product for the orphan indication: treatment of malignant mesothelioma.