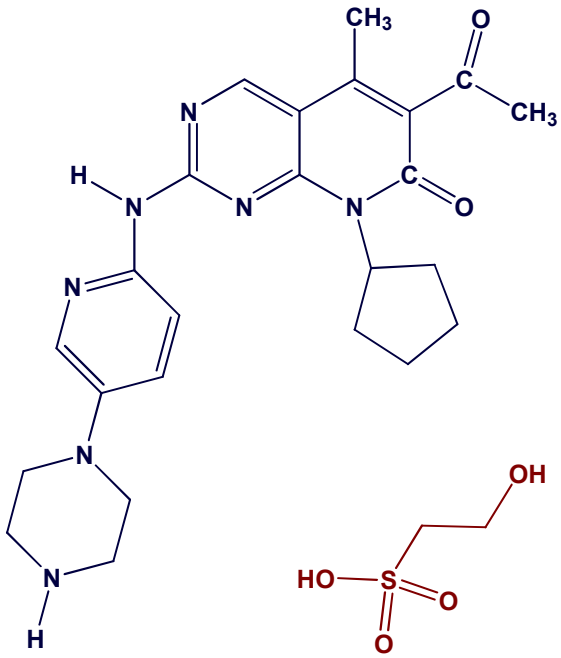
PALBOCICLIB FOR THE TREATMENT OF BREAST CANCER



PALBOCICLIB Hydroxyethanesulfonate
6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one 2-hydroxyethanesulfonate
Chemical Formula: $C_{26}H_{35}N_7O_6S$
Exact Mass: 573,24
Molecular Weight: 573,66
m/z: 573.24 (100.0%), 574.24 (29.6%), 575.24 (6.1%), 575.23 (4.6%), 574.23 (2.6%), 576.24 (1.8%)
Elemental Analysis: C, 54.44; H, 6.15; N, 17.09; O, 16.73; S, 5.59

A recent clinical study, published in April 2014, showed that Palbociclib, a drug developed by the U.S. multinational Pfizer, halved the risk of the worsening of diagnosed breast cancers. These results were shown during a phase II clinical trial: the average time for cancer progression was 20.2 months in the group treated with the drug; almost twice that observed in the control group (treated with habitual drugs).

The most common type of breast cancer is ductal carcinoma. This occurs in the epithelial lining of the ducts that carry milk from the lobules of the breast to the nipple. More rarely, lobular carcinoma, which develops in the breast lobules, also occurs. In both types of cancer (ductal and lobular), malignant tissue eventually extends throughout the entire breast, including the lymph nodes - usually the first sign of inflammation that causes women to seek medical evaluation.

Palbociclib (formulated with hydroxyethanesulphonic acid), prolonged the survival of patients, although not in a statistically significant way: women treated with Palbociclib lived an average of 37.5 months from the commencement of the study, while survival was 33.3 months in the control group.

The results of this study (phase II) were presented at the annual symposium of the American Association for Cancer Research. The data presented was not only followed with keen interest by oncologists, but also by financial analysts on Wall Street; as Palbociclib is considered a potential blockbuster, and a promising innovation for the U.S. multinational Pfizer, with prospective annual sales of billions of dollars. Pfizer will have to pay 8% of their royalties to Amgen, as both pharmaceutical companies were involved in the development of the drug.

But these expectations may be exaggerated because the conclusions at the end of the phase II clinical trial were not as striking as those provisionally announced during the research. At this point, the time during which no tumour progressed was 26.2 in the group treated with Palbociclib as opposed to 7.5 months in the control group.

Richard Finn's arguments to explain the reason why the difference in survival was not statistically significant, was that 61 out of 165 patients died during the course of the trial, and also, patients who abandoned the study, for various reasons, changed to other treatments. These facts partially skew the results of the study using Palbociclib.

Palbociclib slows down the progression of cancer cells by inhibiting the action of two enzymes involved in mitosis: cyclin-kinase type 4 and 6 [1].

Two other Pharmaceutical Companies, Eli Lilly and Novartis AG, have also announced partial results with others drugs that inhibit cyclin-kinase 4/6 (abbreviated as CDK4/6). [CDK enzymes regulate cell proliferation and coordinate checkpoints that repair the structural damage to DNA]. These drugs, which act by inhibiting enzymes CDK4/6, are the first manifestation of a novel mechanism of action. These new drugs focus initially on the treatment of breast cancer, although they are also being tested on other types of cancer.

Some reviewers of the study using Palbociclib say that the results may be biased due to the fact that some researchers knew which patients were being treated with the drug, which would not have allowed the study to be "double-blind" *sensu stricto*).

The community of oncologists stated that other studies are necessary to guarantee the unquestioned credibility of the results presented. The trial has not had sufficient pivotal weight to modify clinical *praxis* protocols in treating breast cancer.

The Pfizer-sponsored study involved 165 postmenopausal women whose treatment for breast cancer was due to either recurrence or metastasis. The cancers were oestrogen-receptor positive, but negative for Her2 (Human Epithelial Receptor type 2). Between 60% and 65% of breast cancers comply with the criteria described above - positive oestrogen receptor [HER+] and Her2 negative.

All women in the study (a study group and a control group) were treated with letrozole [2], a drug that blocks oestrogen synthesis. "Oestrogen receptor inhibitors" are used as the initial treatment for most breast cancers. Half the women in the trial (a study group) also took Palbociclib orally for 3 consecutive weeks, followed by 1 week off (washout).

The most important adverse effect experienced by about 3 out of 4 patients was leukopenia. However, an increase in the number of infections, a common consequence of the clinical condition of leucopenia, was not observed. As a result of this, tolerance to Palbociclib was estimated as "very acceptable". However, it was necessary to reduce the daily dose of Palbociclib in some women, and 13% of those included in the drug-treated study group discontinued the study because of adverse effects; a percentage that was only 2% in the control group.

An important issue is whether Pfizer will gain approval for the drug on the basis of the results of this trial. The Food and Drug Administration usually requires extensive phase III studies, but sometimes make exceptions for certain cancers and other serious illnesses.

If Pfizer finally obtains approval for Palbociclib, the drug could be available on the pharmaceutical market next year (2015). If the FDA rejects the application for approval, Pfizer will have to conduct phase III clinical trials (already in progress, in fact), and marketing will be delayed for a couple of years.

At present (July 2014), several phase III clinical trials, where Palbociclib is being compared to Letrozole (phase III study DOVE-2 [3]), are underway, and Fulvestrant [4] is also being compared to Palbociclib (phase III study DOVE-3[5]). In both studies, women suffering metastatic breast cancer are included.

In another phase III trial, Palbociclib is being contrasted with standard endocrine therapy (PENELOPE-B study [6]) for breast cancer in its early stages.

In 2008, the American F.D.A. gave swift approval for Avastin® (Bebacizumab) by Genentech, another classic treatment of breast cancer, based on the results of a study in which a 5-month delay in the progression of the disease was observed.

The F.D.A. retracted this premature decision [7]: in 2011 it revoked its approval of Avastin® (bevacizumab) for the treatment of breast cancer, after several post-marketing studies demonstrated that the delay in the progression of the disease was less evident than initially estimated.

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