NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2022

Paclitaxel with Encequidar for advanced breast cancer

Company/Developer	Athenex Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 20626	NICE ID: 10760	UKPS ID: 664705

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Oral paclitaxel with encequidar is in clinical development for advanced breast cancer. Advanced breast cancer is a type of breast cancer that has spread to another part of the body. Survival outcomes for patients with advanced breast cancer are poor and current chemotherapy options, including intravenous (IV) administration of paclitaxel, are associated with adverse side effects. Therefore, there is a need for additional therapies for these patients.

Upon oral administration, encequidar blocks the effect of P-glycoprotein, a protein in the body that helps remove foreign substances from cells. It is expected that the medicinal product will allow the cancer medicine paclitaxel to work when given by mouth, helping it pass through cells in the gut and then into other cells such as cancer cells. This is expected to allow paclitaxel by mouth to enter cancer cells in sufficient quantity to slow down the growth of sarcomas and cause fewer side effects than paclitaxel given by infusion into a vein. Therefore, if licensed, paclitaxel with encequidar will offer an additional treatment option for patients with metastatic breast cancer.

Proposed Indication

Patients with advanced breast cancer.[a]

Technology

Description

Encequidar (HM-30181) is an inhibitor of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter P-glycoprotein (P-gp), with adjuvant activity. Upon oral administration, encequidar selectively binds to and inhibits the multidrug resistance (MDR) efflux pump P-gp, which prevents the efflux of various chemotherapeutic agents from intestinal epithelial cells to the gastrointestinal tract. This leads to an increase in both oral bioavailability and therapeutic efficacy. P-gp prevents the intestinal uptake and intracellular accumulation of various cytotoxic agents. Encequidar is not systemically absorbed.[1]

Taxanes such as paclitaxel, are widely used antineoplastic agents with activity in multiple solid tumours including breast. Paclitaxel has low oral bioavailability due to structural instability in the gastrointestinal tract, active extrusion from enterocytes by P-gp and first pass metabolism by liver enzymes CYP3A4 and CYP2C8. However, paclitaxel's absorption is enhanced in P-gp knockout mice and can be administered orally to patients, when given with the highly specific, potent P-gp inhibitor encequidar.[2]

Paclitaxel with encequidar is currently in clinical development for female adult patients with metastatic breast cancer. In a phase III clinical trial (NCT02594371) the paclitaxel capsules are administered with encequidar which is supplied as a 15-mg tablet.[3]

Key Innovation

The addition of encequidar would enable oral administration of paclitaxel which could be more convenient, less resource intensive, and more tolerable than intravenous (IV) administration.[2]

The phase III trial (NCT02594371) has demonstrated that oral paclitaxel with encequidar is the first orally administered paclitaxel shown to be superior to IV paclitaxel for confirmed response, progression-free survival, and overall survival, with minimal clinically meaningful neuropathy.[4] Furthermore, encequidar increases bioavailability of paclitaxel meaning that the medicinal product is more likely to become completely available to its intended biological destination(s).[5,6] Therefore, if licensed, paclitaxel will offer an additional treatment option for patients with metastatic breast cancer.

Regulatory & Development Status

Oral paclitaxel with encequidar does not currently have Marketing Authorisation in the EU/UK for any indication.

Paclitaxel (IV) is licensed in the UK for the following indications:[7]

- Ovarian cancer
- Metastatic ovarian cancer where platinum-containing therapy has failed
- Locally advanced breast cancer
- Metastatic breast cancer
- Adjuvant treatment of node-positive breast cancer following treatment with anthracycline and cyclophosphamide

[a] Information provided by Athenex Inc

- Treatment of non-small cell lung cancer when surgery or radiotherapy not appropriate
- Treatment of advanced acquired immune deficiency syndrome related Kaposi's sarcoma where liposomal anthracycline therapy has failed
- Monotherapy of metastatic breast cancer when first-line treatment has failed and standard, anthracycline-containing therapy is not indicated
- First-line treatment of metastatic adenocarcinoma of the pancreas

Oral paclitaxel with encequidar is also in phase II clinical development for cutaneous angiosarcoma.[8]

The oral formulation of paclitaxel with encequidar has received Promising Innovative Medicine (PIM) award in 2017.[9] Also, oral paclitaxel and encequidar was granted orphan designations for the treatment of soft tissue sarcoma by the European Medicines Agency (EMA) in October 2019.[10]

Patient Group

Disease Area and Clinical Need

Advanced breast cancer (also called stage 3 and 4) is breast cancer that has spread to another part of the body, most commonly the liver, brain, bones, or lungs. Cancer cells can break away from the original tumour in the breast and travel to other parts of the body through the bloodstream or the lymphatic system, which is a large network of nodes and vessels that works to remove bacteria, viruses, and cellular waste products.[11,12] The exact causes of breast cancer are not fully understood. However, there are certain factors known to increase the risk of breast cancer. These include: age; a family history of breast cancer; a previous diagnosis of breast cancer; a previous non-cancerous (benign) breast lump; being tall, overweight or obese; and drinking alcohol. The first symptom of breast cancer that most women notice is a lump or an area of thickened tissue in their breast. Other signs or symptoms of breast cancer include: a change in the size or shape of one or both breasts; a discharge of fluid from either of the nipples; a lump or swelling in either of the armpits; a change in the look or feel of the skin, such as puckering, dimpling, a rash or redness; a rash (like eczema), crusting, scaling or itchy skin or redness around the nipple; or a change in the appearance of the nipple (e.g. becoming sunken into the breast).[13]

Breast cancer is the most common type of cancer in the UK. Most women diagnosed with breast cancer are over the age of 50, but younger women can also get breast cancer.[13] There are around 11,500 breast cancer deaths in the UK every year (2016-2018). Breast cancer is the 4th most common cause of cancer death in the UK, accounting for 7% of all cancer deaths (2018).[14] Breast cancer incidence is strongly related to age, with higher incidence rates observed with increasing age. In the UK, 24% of new breast cancer cases were in people aged 75 and older. The highest incidence rates were observed in those aged 90 years and older amongst females and 85-89 amongst males.[15] In England and Wales (2020-21), there were 202,340 finished consultant episodes (FCE) for malignant neoplasm of the breast (ICD-10 code C50), of which 955 were for male patients and 201,314 were for female patients. This resulted in 199,266 admissions, 172,062 day cases and 47,613 FCE bed days.[16] In England (2017) there were 2,372 patients diagnosed with stage 4 breast cancer.[17]

Recommended Treatment Options

NICE recommends gemcitabine in combination with paclitaxel, within its licensed indication, as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[18] NICE also recommends endocrine therapy for treating people with invasive breast cancer.[19]

Eribulin is also recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:[20]

- it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)
- the company provides eribulin with the discount agreed in the patient access scheme.

Clinical Trial Information

Trial	NCT02594371; An Open-Label, Randomized, Multicenter, Phase 3 Study to Determine the Safety, Tolerability, and Tumour Response of Oraxol and Its Comparability to IV Taxol or Generic IV Paclitaxel in Subjects With Metastatic Breast Cancer **Phase III** – Active, not recruiting **Location(s):** Countries in Latin America **Primary Completion date:** July 2019
Trial Design	Randomised, parallel assignment, open-label
Population	N=402; Subjects with histologically or cytologically confirmed breast cancer for whom IV paclitaxel (as Taxol or generic) monotherapy has been recommended by their oncologist; women ≥18 years of age.
Intervention(s)	Oraxol (oral paclitaxel with encequidar)
Comparator(s)	IV paclitaxel
Outcome(s)	Primary outcome: tumour response as determined by response criteria [Time frame: 19 to 22 weeks] See trial record for full list of other outcomes
Results (efficacy)	For the intention-to-treat (ITT) population, final analysis of the primary endpoint of confirmed tumour response demonstrated a statistically significant difference between treatments; P-glycoprotein pump inhibitor encequidar (Pac+E) 35.8% vs Intravenous paclitaxel (IV Pac) 23.4%, a difference of 12.4%, p=0.011, favouring Pac+E. For the protocol defined mITT population (baseline evaluable scans and received at least 75% of the first cycle of dosing) the confirmed response rates were 40.4% for Pac+E vs 25.6% for IV Pac (p=0.005). For the population with evaluable post-baseline scan, the confirmed response rates were 50.3% for Pac+E vs 29.6% for IV Pac (p=0.0005). Tumour response in all clinically important subgroups was consistent with the overall confirmed response profiles. Responses were durable. Ongoing analysis of duration of confirmed response showed the median durations were 39.0 weeks for Pac+E vs 30.1 weeks for IV Pac. [4] In the ITT population, the median progression-free survival (PFS) was 8.4 months and 7.4 months for the combination and IV paclitaxel, respectively (HR, 0.768; 95% CI, 0.584-1.01; P = .0459). Moreover, the median overall survival (OS) was 22.7 months and 16.5 months, respectively (HR, 0.794; 95% CI, 0.607-1.037; P = .0821).[21]

Results (safety)	The Pac+E group had a lower incidence of alopecia and a lower incidence and severity of neuropathic AEs compared to IV Pac (17% versus 57% respectively to week 23), with Grade 3 neuropathic symptoms observed in 1% for Pac+E vs 8% for IV Pac. The toxicity profile of Pac+E was generally similar to IV Pac. However higher rates of neutropenia, infection and gastrointestinal AEs were observed in Pac+E group. The risk of serious AEs on both treatments was highest among subjects with pre-treatment evidence of hepatic impairment and the protocol was amended to address this issue.[4]

Estimated Cost

Cost of oral paclitaxel with encequidar was confidential at the time of producing this briefing.

NHS indicative prices for paclitaxel IV 100mg/16.7ml concentrate for solution for infusion vials are:[7]

- £200.35 (Hospital only) (Accord Healthcare Ltd)
- £392.82 (Hospital only) (Fresenius Kabi Ltd)
- £374.00 (Hospital only) (Pfizer Ltd)
- £87.50 (Hospital only) (Seacross Pharmaceuticals Ltd)

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Gemcitabine for the treatment of metastatic breast cancer. January 2007
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017.
- NICE cancer service guideline. Improving outcomes in breast cancer (CSG1). August 2002.
- NICE quality standard. Breast cancer. (QS12). June 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer ABC 5). 2020.[22]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[23]

Additional Information

References

1 PubChem. *Encequidar.* Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Encequidar [Accessed 9 February 2022].
2 Jackson CGCA, Hung T, Segelov E, Barlow P, Prenen H, McLaren B, et al. Oral paclitaxel with encequidar compared to intravenous paclitaxel in patients with advanced cancer: A randomised crossover pharmacokinetic study. *British Journal of Clinical Pharmacology*. 2021;87(12):4670-80. Available from: https://doi.org/10.1111/bcp.14886.
3 ClinicalTrials.gov. *Ph3 Study To Determine Safety,Tolerability&Tumor Response Of Oraxol Compared To Taxol In Metastatic Breast Cancer.* 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02594371 [Accessed 9 February 2022].
4 Umanzor G, Cutler DL, Barrios FJ, Vassallo RH, Chivalan MA, Bejarano SA, et al. Abstract GS6-01: Oral paclitaxel with encequidar: The first orally administered paclitaxel shown to be superior to IV paclitaxel on confirmed response and survival with less neuropathy: A phase III clinical study in metastatic breast cancer. *San Antonio Breast Cancer Symposium*. 2020. Available from: https://www.abstractsonline.com/pp8/#!/7946/presentation/2050.
5 Medscape. *paclitaxel/encequidar (Pending FDA Approval).* Available from: https://reference.medscape.com/drug/oraxol-paclitaxel-encequidar-4000132#0 [Accessed 9 February 2022].
6 Price G, Patel DA. Drug Bioavailability. *StatPearls [Internet]*. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557852/.
7 NICE. *Paclitaxel.* Available from: https://bnf.nice.org.uk/drug/paclitaxel.html [Accessed 9 February 2022].
8 ClinicalTrials.gov. *Oraxol | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* Available from: https://clinicaltrials.gov/ct2/results?term=oraxol&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 9 February 2022].
9 PharmaTimes. *New partnership to test oral paclitaxel.* 2019. Available from: https://www.pharmatimes.com/news/cancer_research_uk_trial_paclitaxel_orally_1274391 [Accessed 9 February 2022].
10 European Medicines Agency (EMA). *EU/3/19/2207: Orphan designation for the treatment of soft tissue sarcoma* Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3192207 [Accessed 9 March 2022].
11 BreastCancer.org. *Metastatic Breast Cancer.* Available from: https://www.breastcancer.org/symptoms/types/recur_metast [Accessed 11 February 2022].
12 Healthline. *What is advanced breast cancer?* 2021. Available from: https://www.healthline.com/health/breast-cancer/advanced-breast-cancer#outlook [Accessed 22 March 2022].
13 NHS. *Breast cancer in women.* Available from: https://www.nhs.uk/conditions/breast-cancer/ [Accessed 11 February 2022].
14 Cancer Research UK. *Breast cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Two [Accessed 11 February 2022].
15 Cancer Research UK. *Breast cancer incidence (invasive) statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One [Accessed 11 February 2022].
16 NHS Digtal. *Hospital Admitted Patient Care Activity 2020-21.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 11 February 2022].
17 National Cancer Registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2017.* 2017. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 11 February 2022].

18 NICE. *Managing advanced breast cancer.* Available from: https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181 [Accessed 11 February 2022].

19 National Institute for Health and Care Excellence (NICE). *Early and locally advanced breast cancer: diagnosis and management.* 2018. Available from: https://www.nice.org.uk/guidance/ng101/chapter/recommendations [Accessed 22 March 2022].

20 National Institute for Health and Care Excellence (NICE). *Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen.* 2018. Available from: https://www.nice.org.uk/guidance/ta515/chapter/1-Recommendations [Accessed 22 March 2022].

21 Cancer Network. *Oral Paclitaxel, Encequidar Continues to Improve OS in Metastatic Breast Cancer.* 2020. Available from: https://www.cancernetwork.com/view/oral-paclitaxel-encequidar-continues-to-improve-os-in-metastatic-breast-cancer [Accessed 16 March 2022].

22 Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology*. 2020;31(12):1623-49. Available from: https://doi.org/10.1016/j.annonc.2020.09.010.

23 Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2018;16(3):310-20. Available from: https://doi.org/10.6004/jnccn.2018.0012.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.