20 March 2014
EMA/CHMP/691219/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Neocepri

International non-proprietary name: folic acid

Procedure No.: EMEA/H/C/002773/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This AR reflects the CHMP opinion on 20 March 2014, which originally recommended to approve this medicine. The recommendation was conditional to the results of the on-going confirmatory study EC-FV-06. Before the marketing authorisation was granted by the EC, the results of this study became available and did not support the initial recommendation. Subsequently, the company decided to withdraw the application and not to pursue any longer the authorisation for marketing this product. The current report does not include the latest results of this study as the withdrawal of the application did not allow for the CHMP to revise its opinion in light of the new data.

For further information please refer to the Q&A which followed the company's withdrawal of the application.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5505
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

5MTHF	5-methyl-tetrahydrofolate
^{99m}Tc	metastable form of technetium (^{99m}Tc)
^{99}Tc	technetium-99 (^{99}Tc)
^{99m}Tc-etarfolatide	technetium-99m etarfolatide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CL	Clearance
Cmax	maximum concentration
CNS	central nervous system
CPM	counts per minute
CYP	cytochrome P-450
DAVLBH	desacetylvinblastine hydrazide
DDI	drug-drug interaction
DHFR	dihydrofolate reductase
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DTPA	diethylenetriaminepentaacetic acid
EC145	vintafolide
EC20	etarfolatide; folate-targeting imaging agent; Pteroyl-γGlu-βDpr-Asp-Cys
EFSA	European Food Safety Authority
FA	folic acid; folate
FR	folate receptor
GLP	Good Laboratory Practice
HDFA	high-dose folic acid
HR	hazard ratio
IC_{50}	50% maximal inhibitory concentration; the concentration required to kill 50% of the treated cells
%ID/g	percent injected dose per gram of tissue
IM	Intramuscular
IV	intravenous, intravenously
K_d	dissociation constant
K_m	Michaelis constant; binding affinity
LPT	lightly pretreated
mCi	Millicurie
µg	Microgram
mg/d	milligram per day
MRI	magnetic resonance imaging
MTX	Methotrexate
MVI	Multivitamin
NA	not applicable
ng h/ml	nanogram hours per ml

NSCLC	non-small cell lung cancer
PBS	phosphate buffered saline
PLD	pegylated liposomal doxorubicin; Doxil®; Caelyx®
PROC	platinum resistant ovarian cancer
RA	rheumatoid arthritis
RFC	reduced folate carrier
SC	Subcutaneous
SCF	Scientific Committee on Food
SCS	summary of clinical safety
SPECT	single photon emission computed tomography
T:NT	tumour-to-non-tumour
µCi	Microcuries

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Endocyte Europe, B.V. submitted on 26 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Neocepri, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2012.

Neocepri had been designated as an orphan medicinal product EU/3/12/1044 on 10 September 2012. Neocepri was designated as an orphan medicinal product in the following indication: Diagnosis of positive folate receptor in ovarian cancer.

The applicant applied for the following indication: This medical product is for diagnostic use only. Neocepri is administered prior to Folcepri, a folate receptor (FR) targeted radiodiagnostic imaging agent. Neocepri is indicated for the enhancement of Folcepri single photon emission computed tomography (SPECT) image quality.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Folic acid was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0248/2012 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

Study EC-FV-04 was a randomised, multicentre, open-label phase 2 study, in which patients with platinum resistant ovarian cancer (PROC) received treatment with vintafolide in combination with pegylated liposomal doxorubicin (PLD) versus PLD alone. In this study, patients underwent ^{99m}Tc-etarfolatide imaging after injection of 0.5 mg of folic acid and the ^{99m}Tc-etarfolatide uptake was evaluated for each patient before starting study treatment. Results of study EC-FV-04 showed a statistically significant reduction in the risk of progression or death and an associated clinically meaningful difference in median PFS compared to the PLD alone arm. The efficacy was related to folate receptor (FR) expression, with the greatest benefit observed in the population with the worse prognosis, the population who express the folate receptor on all target lesions [FR(100%)] as assessed by etarfolatide. Conversely, no benefit was observed in patients who had 0% FR positive lesions [FR(0%)]. Folic acid as a pre-injection for ^{99m}Tc-etarfolatide has demonstrated the ability to enhance the images to effectively select patients with the worse prognosis (FR(100%) population), thereby personalising vintafolide treatment for those patients most likely to benefit.

Balanced against the outlined benefit, the safety profile of folic acid, which is mainly based on bibliographic references indicate it is well-tolerated.

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

Additional comprehensive data are likely to be available from the ongoing phase 3 study EC-FV-06, a randomised double-blind phase 3 trial comparing vintafolide and PLD in combination versus PLD in patients with PROC. The study has been designed to confirm and support the benefit-risk balance in the 100% FR-positive PROC patient population. The primary analysis for Study EC-FV-06 will compare PFS (based on RECIST V 1.1 criteria) in patients with platinum-resistant ovarian cancer with all target lesions ^{99m}Tc-etarfolatide positive [FR(100%)] who receive combination therapy with vintafolide and PLD to patients with platinum-resistant ovarian cancer who receive PLD and placebo. Additional analyses will evaluate the lower FR positive levels. A total of up to approximately 600 FR positive patients are expected to be enrolled in the study, with approximately 350 of those being FR(100%) patients. Additional data from this study are expected to further define the clinical utility of pre-injection of folic acid prior ^{99m}Tc-etarfolatide scan for selection of patients for treatment with the vintafolide in combination with PLD in a larger subset of patients.

- Unmet medical needs to be fulfilled.

PROC is an orphan condition with a high unmet medical need. Patients with PROC have very few therapeutic options. Importantly, the subset of women whose disease expresses the FR

represents an epidemiologically small subset of PROC and an area of high unmet medical need, with an overall worse prognosis and no approved agents for selection or treatment.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweigh the risk inherent in the fact that additional data are still required.

The available data indicate a positive risk-benefit balance for pre-injection of folic acid prior ^{99m}Tc-etarfolatide scan. Given the available results of the pivotal trial, the timelines of completion of study and in view of the unmet medical need, the benefits to public health of the immediate availability on the market of the medicinal product concerned outweigh the risk inherent in the fact that additional data are still required.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 14 April 2011, 19 May 2011 and 22 September 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

The manufacturing sites comply with the EU Good Manufacturing Practice requirements.

Manufacturer responsible for batch release

Almac Pharma Services
Seagoe Industrial Estate, Craigavon, BT63 5UA
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

- The application was received by the EMA on 26 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 February 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013.
- During the PRAC meeting on 7 March 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of

Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 March 2013.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 September 2013.
- The summary report of the GCP inspection carried out between 22 April 2013 and 23 May 2013 at one site in Poland, one site in the United States and the sponsor site, was issued on 5 July 2013.
- The summary report of the GMP inspection carried out at one manufacturing site, between 22 and 26 July 2013 was issued on 21 august 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 October 2013.
- During the PRAC meeting on 7 November 2013, the PRAC adopted Rapportuer's Risk Management Plan Assessment Report.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 January 2014.
- During the PRAC meeting on 9 January 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 23 January 2014 the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 29 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 February 2014
- During the CHMP meeting on 18 February 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 March 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Neocepri.

2. Scientific discussion

2.1. Introduction

Problem statement

An estimated 225,000 new cases of ovarian cancer were reported worldwide in 2008. In Europe, an estimated 65,538 new cases of ovarian cancer were reported in 2012 with 42,704 deaths (EUCAN Cancer factsheets: Ovary). Ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death in women. Epithelial ovarian carcinoma is the most common ovarian cancer accounting for approximately 90% of cases.

Several factors appear to affect the risk of developing ovarian cancer. 50% of cases occur in women older than 65 years. Approximately 5% to 10% of ovarian cancers are familial. The most important risk factor for ovarian cancer is a family history of a first-degree relative (e.g., mother, daughter, or sister) with the disease. Women who have had multiple pregnancies appear to have a lower risk than those with fewer pregnancies.

The most common symptoms of ovarian cancer arise from peritoneal spread and include abdominal pain, bloating, abdominal swelling (mainly due to ascites), nausea, anorexia and weight loss.

Prognosis factors include the histological grade and subtypes as well as the stage of the disease at diagnosis. The presence or absence of residual disease at the completion of the initial surgery, the patient's functional status and age, and the use or non-use of platin-based chemotherapy are also prognostic factors.

The FIGO (International Federation of Gynaecology and Obstetrics) staging system is used to classify the extent of disease and provide the basis for treatment considerations. According to the FIGO staging system, patients with newly diagnosed Stage I or II disease have limited ovarian carcinoma confined to the ovaries and pelvis; Patients diagnosed with Stage III or IV disease have advanced ovarian carcinoma that is intraperitoneal (IP) or involves distant metastases. Management of ovarian carcinoma depends on the extent of disease and prior therapy that the patient has received.

Advances in optimisation of cytoreductive surgery and platinum-based chemotherapy have resulted in a 5-year survival rate of approximately 45% (Bookman, 2005). Unfortunately, the majority of patients diagnosed with ovarian cancer will eventually develop disease that is resistant to platinum-based therapy. Women who initially respond to platinum-containing systemic therapy but progress after a treatment-free interval of less than 6 months are considered to have platinum-resistant ovarian cancer. Platinum resistant ovarian cancer has a poor prognosis and patients have limited therapeutic options: topotecan, paclitaxel, pegylated liposomal doxorubicin (PLD). Other therapeutic options are urgently required to address the unmet medical need.

About the product

Folate (vitamin B9) is required by cells for normal metabolic activity as well as for DNA synthesis, and therefore essential for cell division. Folate is internalised by cells via two distinct mechanisms. The first is through the reduced folate carrier (RFC), a membrane transporter, present on almost all normal cells, that shuttles folate into the cell via a low affinity mechanism (Km~200 µM). The second mechanism involves the high affinity (Kd <1 nM) membrane folate receptor (FR) protein, which is expressed on many highly proliferative cancer cells. Following tight binding, internalisation, and a conformational change-induced intracellular release of folate, the receptor returns to the cell surface to resume its activity. The RFC is found in virtually all cells and constitutes the primary pathway responsible for uptake of physiological folates. The FR is found primarily on polarised epithelial cells and activated macrophages, and preferentially binds and internalises oxidised folates via receptor-mediated endocytosis. While low concentrations of the reduced folate carrier are probably

sufficient to supply the folate requirements of most normal cells, the FR is frequently over-expressed on cancer cells, enabling the malignant cell to compete successfully for the vitamin when supplies are limited. At least three forms of the FR have been described (alpha, beta, gamma and truncated gamma).

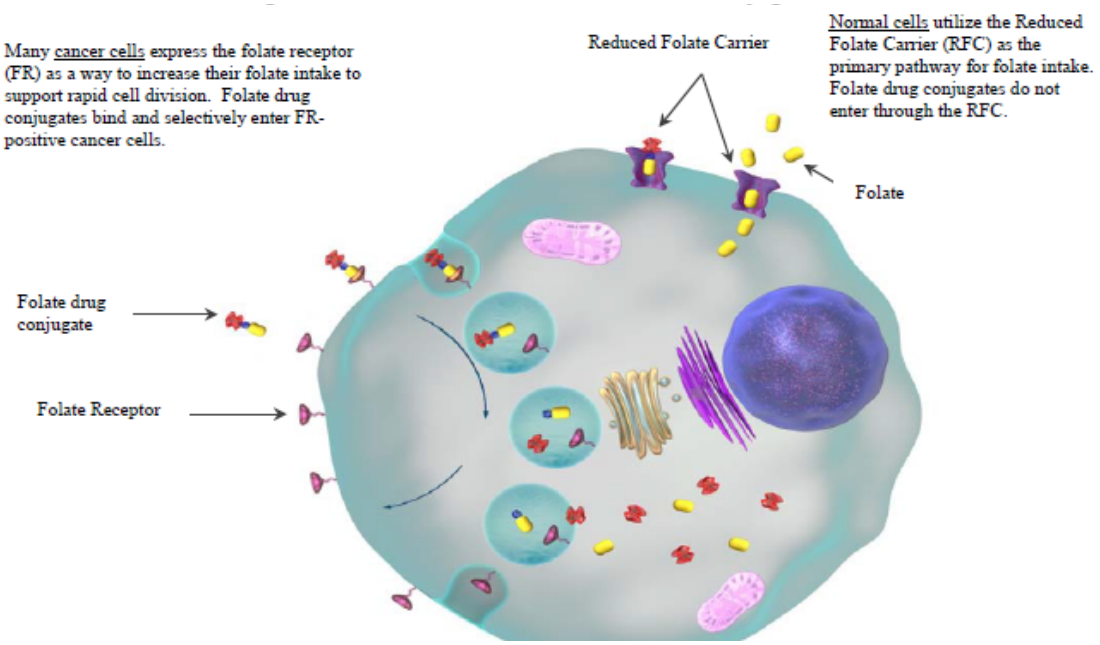


Figure 1: Mechanism of action of folate conjugates

A large number of cancers express high levels of the FR (Parker, 2005; Reddy, 2006; Vlahov, 2006; Leamon, 2007; Reddy, 2007) and FR expression is often associated with a worse overall prognosis. In ovarian cancer specifically, FR expression is known to increase with cancer stage, grade, and platinum resistant phenotype and be associated with a faster PFS and shorter OS (Toffoli, 1997; Toffoli, 1998; Chen, 2012).

There is currently no radiopharmaceutical imaging agent approved in the EU that utilises the FR as a pharmacological target for diagnostic purposes.

Etarfolatide (also referred as EC20) is composed of a ^{99m}technetium chelating peptide covalently bonded to folic acid. The folic acid moiety is proposed to function as a targeting ligand that binds to folate receptors that may be present on the surface of many cancer cells. The peptide moiety of etarfolatide functions as a chelator of certain transition metals including ^{99m}technetium (^{99m}Tc). When formulated, ^{99m} Tc-etarfolatide is administered intravenously for the purpose of anatomically identifying malignant lesions that express functional folate receptors (FR). Positive lesion uptake of ^{99m} Tc-etarfolatide is a prerequisite for the administration of companion folate-targeted therapeutics, such as vintafolide (EC145, a folate-vinca alkaloid conjugate).

Tumour imaging with ^{99m}Tc-etarfolatide can be performed soon after administration since it reaches the tumour rapidly and is quickly cleared from the blood. However, while FR expression in most normal tissues is very low or undetectable when compared with FR-positive cancers, background uptake can occur, reducing the quality of the image. As a way to improve imaging, a small amount of pre-dosed folic acid, which in its un-metabolised form is the highest affinity ligand for the folate

receptor, was found to enhance the quality of tumour images by competitively blocking background uptake in normal tissues.

Folic acid is to be used prior to the administration of the diagnostic imaging agent ^{99m}Tc-etarfolatide to improve image quality.

The applied indication was: This medical product is for diagnostic use only. Neocepri is administered prior to Folcepri, a folate receptor (FR) targeted radiodiagnostic imaging agent. Neocepri is indicated for the enhancement of Folcepri single photon emission computed tomography (SPECT) image quality.

Following review, the final indication for Neocepri proposed was:

This medicinal product is for diagnostic use only. Neocepri is administered prior to ^{99m}Tc-etarfolatide, a folate receptor (FR) targeted radiodiagnostic imaging agent for use in ovarian cancer. Neocepri is indicated for the enhancement of ^{99m}Tc-etarfolatide single photon emission computed tomography (SPECT) image quality.

2.2. Quality aspects

2.2.1. Introduction

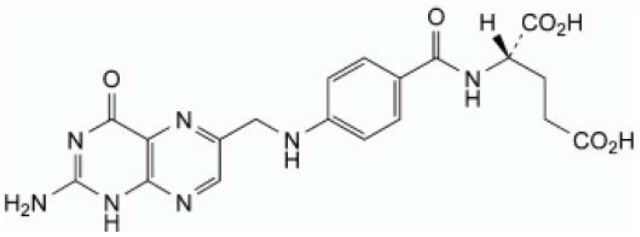
The finished product is presented as solution for injection containing 1 mg of folic acid in one ml of solution as active substance.

Other ingredients are: disodium edetate, sodium hydroxide (for pH adjustment) and water for injections.

The product is available in glass vial with a Flurotec-coated chlorobutyl rubber stopper and an aluminium seal.

2.2.2. Active Substance

The chemical name of folic acid is (2*S*)-2-[(4{[(2-amino-4-hydroxypteridine-6-yl)methyl]amino}phenyl)formamido]pentanedioic acid and it has the following structure:



Folic acid is a yellowish or orange, crystalline powder, practically insoluble in water and in most organic solvents.

As there is a monograph of folic acid in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

Manufacture

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for: appearance, identity (HPLC, Optical rotation), water (Ph Eur), sulphated ash (Ph Eur), related substances (Ph Eur), assay (Ph Eur), residual solvents (GC) and microbial content (Ph Eur).

The control tests were carried out to comply with the specifications and test methods of the Ph Eur Monograph, as confirmed by the CEP.

Batch analysis data of 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Reference is made in the CEP, where a suitable re-test period in a defined container closure system is provided.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The pharmaceutical development was based in already approved folic acid finished products. The active substance folic acid is described in the Ph. Eur and a CEP has been provided.

The main excipients used are water for injections and disodium edetate.

The manufacturing process is comprised of dissolution and mixing. Process development therefore consisted of the production of engineering/pilot batches and process validation batches. No significant changes were made to the manufacturing process during development. Different sterilization methods were investigated as recommended in the Note for Guidance on Development Pharmaceutics CPMP/QWP/155/96.

Neocepri is presented in a type I amber glass vial with a chlorobutyl rubber fluorotec-coated stopper and a red flip-off seal. An amber glass vial is used because the product is light sensitive. This is a well-established conventional container closure system for solutions for injection. Integrity testing of the container closure system was performed, and with reference to results of an extractables study using media similar to that of the commercial formulation, it was stated that the risk of leachable impurities to patient safety is considered to be minimal.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of four main steps: preparation of the folic acid solution, bioburden reducing filtration, sterile filtration and filling, stoppering and capping. It is an aseptic process and therefore considered a non-standard process.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data on three consecutive batches of the commercial batch size have been provided It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identity (UV, RPLC), individual specified degradation products (RPLC), individual unspecified degradation product (RPLC), total degradation products (RPLC), assay (RPLC), pH (potenciometric), uniformity of dosage units (Ph Eur), sterility (Ph Eur), endotoxin (Ph Eur) and particulate matter (Ph Eur).

Batch analysis results are consistent with the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 6 commercial scale batches of finished product stored under long term conditions for 12 months at 5 ± 3 ºC / Ambient RH and for up to 12 months under accelerated conditions at 25 ± 2 ºC / 60 ± 5% RH according to the ICH guidelines were provided. The batches of Neocepri are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, degradation products, assay, pH, sterility, endotoxin and particulate matter. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Folic acid is a widely used, well-known active substance. No pharmacology, pharmacokinetics, or toxicology studies were submitted as part of the dossier.

Non-clinical studies submitted were limited to studies that were conducted to establish the use of folic acid as a pre-injection agent to enhance diagnostic imaging of etarfolatide for patient selection. An overview of literature date available was also submitted in support of this application.

2.3.2. Pharmacology

Folates and folic acid (pteroylglutamic acid) are essential water-soluble vitamins which fall within the vitamin B group. Folates occur naturally in a variety of foods including leafy green vegetables, certain (citrus) fruits and beans. The fully oxidised folate, folic acid, is a synthetically stable and bioavailable form of this vitamin that is used most often in food supplements, food fortification and pharmaceutical preparations. Folate is an essential nutrient required for cell division.

Tissue uptake of folate predominantly occurs via i) the reduced folate carrier (RFC) protein which is expressed on most normal cells, or ii) through FRs which are overexpressed on epithelial cancer cells but not significantly expressed in normal tissue (Reddy et al, 2007). Folic acid is the ligand which displays the highest known affinity (Kd ~0.1 nM) for the FR, but with a low affinity (Km>200 µM) for the ubiquitously expressed RFC (Leamon et al, 2009).

Following oral intake, folic acid is primarily converted to 5-methyl-tetrahydrofolate (5MTHF), which makes it the primary folate species in circulation after oral administration and this compound has a 14-fold weaker affinity for the FR when compared to un-metabolised folic acid (Lucock et al., 1989a; Lucock et al., 1989b; Selhub et al., 2001). The incomplete metabolism of oral folic acid results in only a very small fraction of the administered dose that will circulate in the form of un-metabolised folic acid, resulting in a much lower plasma concentration of this high affinity molecule when compared to intravenous folic acid. Additionally, the inherent inter-patient differences in oral folic acid absorption rates, as well as intestinal 5MTHF conversion rates, will result in a wide range of levels and percentages of both metabolised and un-metabolised folic acid in circulation (Kelly et al., 1997).

Folic acid is the most stable form of folate, and it is the form used most often in food supplements, food fortification and pharmaceutical preparations. Naturally occurring folates ingested from food are largely de-conjugated (i.e. the poly-gammaglutamyl group is removed) and are then reduced by dihydrofolate reductase within the intestines and liver to form 5–methyltetrahydrofolate, the most predominant form of folate found in the circulation. Folic acid is a poor substrate for dihydrofolate reductase, and in subjects administered oral supplements of more than approximately 260 µg per day, unmetabolised folic acid is observed in the serum (Kelly et al, 1997). This may be a reflection of the slow, or saturable conversion rate of folic acid to tetrahydrofolate in the human liver (Bailey et al, 2009).

In tissues, folates are retained as polyglutamate conjugates which act as cofactors to enzymes that perform methylation reactions, such as in DNA synthesis and amino acid inter-conversions (e.g. the re-methylation of homocysteine to methionine). Folates are therefore essential in normal DNA synthesis/repair and in amino acid metabolism.

Primary pharmacodynamic studies

Three studies on the interaction of folic acid with the FR and impact of folic acid on tumour to non-tumour (T:NT) uptake ratios of ^{99m}Tc-etarfolatide were submitted. These non-clinical studies were conducted to establish the use of folic acid as a pre-injection agent to enhance diagnostic imaging of etarfolatide for patient selection.

Study EC20-B-PR-0032

The binding affinity of ^{3}H-folic acid to FR-positive human nasopharyngeal carcinoma cells (KB cells) was investigated in study# EC20-B-PR-0032.

Cultured KB cells (a FR-positive nasopharyngeal carcinoma with HeLa markers) were incubated with 0.1 to 25 nM ^{3}H-folic acid. Following a 2 hour incubation at 4 or 37 °C, cells were rinsed free of unbound radiolabel and counted for residual cell-associated radioactivity. The quantity of bound radioactivity at 4 and 37 °C was plotted against the concentration of ^{3}H-folic acid and corresponding dissociation constant's (Kd) estimated.

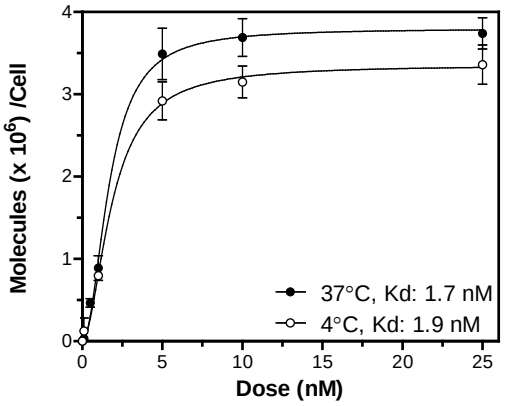


Figure 2: Folate Receptor Affinity of ^{3}H-Folic Acid.

Folic acid was determined to have a high affinity for the FR present on cell membranes (dissociation constant, Kd of 1.7 (4^{o}C); 1.9 nM (37^{o}C) in this system).

Study# EC20-B-PR-0024

The tumour to non-tumour (T:NT) uptake ratios of ^{99m}Tc-etarfolatide were found to improve if a small amount of folic acid was co- or pre-injected into the mice (Reddy et al. 2004). M109 tumour-bearing female Balb/c mice were used to examine the tissue distribution of ~50 µg/kg (67 nmol/kg) ^{99m}Tc etarfolatide in response to escalated doses of co- or 5 min. pre-administered non-radiolabelled folic acid (1, 10 and 100 equivalents). Four hours after administration of ^{99m}Tc-etarfolatide, M109 tumour together with a panel of normal tissues were collected, weighed and then assayed for radioactivity. As shown in the table below, ^{99m}Tc-etarfolatide was found to predominantly concentrate in the FR-positive tumours and kidneys. In addition, with the exception of the FR-positive kidneys, all T:NT ratios increased (including the tumour-to-intestine/bowel ratio) when one equivalent dose of folic acid was administered. Higher amounts of injected folic acid were found to compromise the specific uptake of ^{99m}Tc-etarfolatide in the tumour tissue, which in turn compromised the positive effects on the T:NT ratios (data not shown).

Table 1: Impact of co- or 5 min. pre-injection of Folic Acid on the Tissue biodistribution and Tumour:Non-Tumour Uptake Ratios of ^{99m}Tc-EC20.

	^{99m}Tc-EC20		**^{99m}Tc-EC20 + 1 eq. FA**			
			Co-dose		**Pre-dose**	
	% ID/g	**T:NT**	**% ID/g**	**T:NT**	**% ID/g**	**T:NT**
Blood	0.32 ± 0.11	79.6 ± 15.6	0.08 ± 0.01	213.6 ± 87.5	0.12 ± 0.06	148.0 ± 39.5
Heart	1.89 ± 0.41	13.4 ± 3.5	0.72 ± 0.09	23.0 ± 5.7	0.90 ± 0.40	20.2 ± 7.8
Lung	2.00 ± 0.54	13.2 ± 5.7	0.67 ± 0.04	24.8 ± 7.5	0.73 ± 0.14	22.7 ± 1.3
Liver	4.70 ± 1.01	5.3 ± 0.7	1.84 ± 0.39	9.3 ± 3.3	2.86 ± 0.20	5.7 ± 0.6
Spleen	0.56 ± 0.07	44.7 ± 12.1	0.24 ± 0.01	70.0 ± 18.1	0.40 ± 0.11	43.5 ± 15.3
Intestine	3.91 ± 1.34	6.6 ± 1.8	1.12 ± 0.45	17.9 ± 12.4	2.03 ± 1.34	11.4 ± 7.8
Kidney	175.23 ± 14.97	0.1 ± 0.03	100.89 ± 16.86	0.2 ± 0.1	132.66 ± 20.60	0.1 ± 0.03
Muscle	1.80 ± 0.21	13.6 ± 2.0	0.48 ± 0.13	36.7 ± 15.9	0.82 ± 0.16	20.3 ± 4.2
Stomach	1.45 ± 0.37	18.5 ± 9.6	0.55 ± 0.12	30.0 ± 2.1	0.56 ± 0.26	35.7 ± 22.0
Tumour	24.66 ± 5.95	--	16.51 ± 4.60	--	16.47 ± 2.72	--

T:NT, tumour to non-tumour ratio; %ID/g, percent injected dose per gram of tissue; FA, folic acid.

Study# EC20-B-PR-0015

The impact of co-injected folic acid on tumour:non-tumour (T:NT) tissue ratios was evaluated in nu/nu mice bearing human FR-positive tumour xenografts.

Considering i) that the human dose of ^{99m}Tc-etarfolatide is 100 µg/patient (or 134 nmol/70 kg body mass), and ii) body mass to surface area conversion factor (from human to mouse) is ~14, the "equivalent" mouse ^{99m}Tc-etarfolatide dose level was estimated to be ~27 nmol/kg. Tissue accumulation in normal and tumour tissues following a 27 nmol/kg ^{99m}Tc-etarfolatide dose was maximal when no co-injected folic acid was used. Tissue levels of ^{99m}Tc-etarfolatide progressively decreased with increasing amounts of co-injected folic acid. However, higher T:NT ratios of ^{99m}Tc-etarfolatide generally resulted when co-injected folic acid levels were < 1 mg HED.

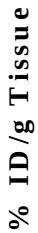


Figure 3: Effect of co-injected folic acid on the 4 hour tissue distribution of ^{99m}Tc-etarfolatide in KB tumour-bearing nu/nu mice

Table 2: Tumour to non-tumour ratios of ^{99m}Tc-etarfolatide in nu/nu mice

HED[a] Dose of Folic Acid	T:NT[b] Tissue Uptake Ratios in Mice				
	Liver	*Lung*	*Heart*	*Spleen*	*Blood*
0	3	5	4	25	24
0.05	4	8	7	23	26
0.25	5	12	12	17	27
0.5	4	8	12	23	21
1	2	4	5	9	6
5	1	2	37	3	3

[a]HED = Human Equivalent Dose expressed in mg per patient; based on allometric scaling from mouse to 70 kg human

[b]Tumour-to-Non Tumour

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were submitted.

Safety pharmacology programme

No safety pharmacology studies were submitted.

Pharmacodynamic drug interactions

No pharmacodynamic studies were submitted.

2.3.3. Pharmacokinetics

No pharmacokinetics studies were submitted.

2.3.4. Toxicology

No toxicology studies were submitted.

2.3.5. Ecotoxicity / environmental risk assessment

Folic acid is a naturally occurring anti-anaemic member of the vitamin B complex. It is a natural component of green leafy vegetables, liver, kidney, milk, shellfish, yeast, fruits and grasses. It is converted to tetrahydrofolic acid, which is required for erythropoiesis, synthesis of purine and thymidylates and metabolism of some amino acids (TOXNET, Hazardous Substances Data Bank, 2012).

A complete Environmental Risk Assessment has not been performed for folic acid, in accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 1*, 1 June 2006) which states that vitamins are exempted because they are unlikely to result in significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

The pharmacodynamic properties of folic acid are well established; therefore no new studies were conducted relative to general pharmacodynamics of folic acid, which is considered acceptable. Two studies on the interaction of folic acid with the FR were conducted to establish the use of folic acid as a pre-injection agent to enhance diagnostic imaging of etarfolatide for patient selection.

The binding affinity of ^{3}H-folic acid to FR-positive human nasopharyngeal carcinoma cells (KB cells) was investigated and folic acid was determined to have a high affinity for the FR present on cell membranes (Kd of 1.9 nM at 37^{o}C). The tumour to non-tumour (T:NT) uptake ratios of ^{99m}Tc-etarfolatide were found to improve if a small amount of folic acid was co- or pre-injected into the mice. ^{99m}Tc-etarfolatide was found to predominantly concentrate in the FR-positive tumours and kidneys and with the exception of the FR-positive kidneys, all T:NT ratios increased when one equivalent dose of folic acid was administered.

This finding might be the result of low levels of FRs in blood and some non-target tissues that become at least partially saturated by the co-formulated free folic acid; thus, only the more highly expressing FR–positive organs (tumour and kidney) would be available to bind ^{99m}Tc-EC20 under these dosing conditions. The implication of this result is that the sensitivity of detecting FR–positive tumours might be improved by varying the mass of free folic acid in the radiotracer formulation (Casper, 2005).

Taken together, the non-clinical studies presented provided a rationale to support the use of a low dose folic acid as a pre-injection to enhance the image quality following ^{99m}Tc-etarfolatide.

No secondary or safety pharmacology studies were conducted. This is considered acceptable since the clinical safety of folic acid is well known and the proposed indication is a single dose of 0.5 mg.

Folic acid is a widely used and well-known vitamin and the pharmacokinetics is well-established. No new pharmacokinetic studies of folic acid were conducted, which is considered to be acceptable. The single i.v administration of 0.5 mg of folic acid at half the recognised upper limit for chronic daily intake is expected to have a predictable pharmacokinetic profile.

No toxicology studies have been submitted with folic acid. As folic acid is a well-known compound with a well-established safety profile in humans this is considered acceptable. Folic acid can be given via multiple routes, at different doses, and for extended periods of time and is administered to adults, pregnant and nursing women, and children. Folic acid given as a single injection of 0.5 mg to adults to enhance diagnostic imaging would likely be considered as a lower risk compared to other doses and schedules that are already well prescribed, and well characterised as having limited risk to patients. Folic acid is non-genotoxic, non-carcinogenic, and does not cause fertility, reproductive, fetal, or developmental toxicity.

Since ^{99m}Tc-etarfolatide is contraindicated in pregnant women, folic acid for the purpose of enhancing image quality should not be administered to pregnant women.

Folic acid is also well-established as not causing local toxicity. Therefore, no local tolerance studies were submitted. Folic acid can be administered safely intramuscularly and subcutaneously, and is not an extravasation hazard.

There have been some case reports of hypersensitivity reactions to folic acid administration, but it cannot be excluded that other components of the formulations were responsible. Even if related to folic acid, these reactions are likely to be very rare (Scientific Committee on Food (SCF), 2000). A warning for use in patients with known hypersensitivity to folic acid is stated in the SmPC.

The active substance, folic acid, is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, folic acid is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

As folic acid is a widely used, well-known active substance, additional pharmacodynamic and pharmacokinetic non-clinical studies, except for two studies on the interaction of folic acid with the FR submitted, are not required. The non-clinical studies performed support the use of a low dose folic acid as a pre-injection to enhance the image quality following ^{99m}Tc-etarfolatide.

Overall, the absence of non-clinical toxicological data is considered acceptable considering the long clinical experience and relatively low dose of folic acid intended to be used (single intravenous injection of 0.5 mg).

In conclusion, folic acid is generally considered safe, and is a well-used, well-established vitamin. Therefore, no additional non-clinical studies are considered required.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3: Tabular overview of clinical studies supporting the use of folic acid pre-injection before ^{99m}Tc-etarfolatide scan in selecting patients for treatment with the therapeutic agent vintafolide

Study Identifier	Study Objective	Study Design and Type of Control	Dosage Regimen	Healthy Subjects or Diagnosis of Patients
EC20.1	Safety, biodistribution, metabolism, protein binding, excretion, and dosimetry	Phase 1, open-label, non randomized, within subject evaluation, single dose	Single intravenous injection of 0.1 mg etarfolatide labelled with 15-20 mCi of ^{99m}Tc. Planar image acquisition at 5 min and 1, 4, 6-8, and 18-24 Hours post-injection. Two (2) of 4 normal volunteers and 2 of 4 ovarian cancer patients received 0.5-2.0 mg folic acid 2-3 min. prior to injection of ^{99m}Tc-etarfolatide.	Normal female volunteers and females with known or suspected ovarian cancer age ≥ 18 years
EC20.11	Safety, biodistribution, excretion, dosimetry	A Phase 1, open-label, Clinical Study to Evaluate the Biodistribution and Safety of ^{99m}Tc-etarfolatide (EC20) in Normal Volunteers	0.5 mg or 1.0 mg IV injection of Folic Acid IV injection of 0.1 mg of etarfolatide labeled with 20 to 25 mCi of ^{99m}Tc-Etarfolatide	Healthy volunteers, age ≥ 18 years of age

2.4.2. Pharmacokinetics

No new pharmacokinetics studies were submitted. The applicant referred to literature data.

Absorption

Not applicable.

Distribution

Folic acid is distributed into plasma and extracellular fluid, and is weakly bound to albumin (70%). Folic acid has a high affinity to the folate receptor, substantially higher than the other folate species folinic acid (leucovorin) and 5MTHF (metabolite of folic acid) (Leamon et al, 2009).

Elimination

Administration of tritiated folic acid to healthy volunteers at three different dose levels was studied by John et al (1961). A very low dose (1 µg/kg) resulted in a very rapid disappearance of folic acid from the blood and but a low fraction found in urine, whereas higher doses resulted in a slower

decline in plasma radioactivity and more renal excretion. After the intravenous administration of 1 µg per kg of tritiated folic acid, the concentration in the plasma fell very rapidly so that after 3 minutes only 2% of the injected dose/L remained, and by 30 minutes only 0.1 to 0.2 % of the injected dose/L remained.

After a 15 µg/kg iv folic acid dose, 30-50% of the radioactivity was found in urine the first days after injection, and about half of this was unchanged folic acid. After a rapid initial distribution, the terminal half-life was >1 hour.

Available pharmacokinetics data for oral folic acid showed that pre-systemic metabolism converts a high fraction of the parent compound to 5-methyltetrafolate, which has less folic acid receptor affinity (Public assessment report, Folic Acid 2.5 mg/5 ml (UK/H/1930/001/DC)). When a folic acid dose <1 mg is administered orally, about 70% is retained in the body and the rest is excreted into urine. The retained folic acid is taken into cells and reduced by dihydrofolate reductase to tetrahydrofolate. Folic acid is a relative poor substrate for folate reduction, the normal substrate being dihydrofolate.

Dose proportionality and time dependencies

Intravenously administered folic acid is known to have dose dependent pharmacokinetics, with a very fast disappearance from the systemic circulation at low doses, and a slower decline in plasma concentration together with a higher fraction of urine excretion at higher doses.

Special populations

No data in special populations were presented.

Pharmacokinetic interaction studies

No pharmacokinetic interaction data were submitted.

2.4.3. Pharmacodynamics

No pharmacodynamic studies data were submitted.

2.4.4. Discussion on clinical pharmacology

No new pharmacokinetic studies have been performed, and the applicant referred to literature data as well as a public assessment report for an authorised oral folic acid solution. The pharmacokinetic data submitted was rather sparse, but this is considered acceptable considering the single administration and the well-known properties of folic acid.

Folic acid is distributed into plasma and extracellular fluid, is weakly bound to albumin and has a high affinity to the folate receptor.

One reference has been submitted describing the pharmacokinetics of intravenously administered folic acid, suggesting that after very low doses a very rapid disappearance of radioactivity from the blood can be observed, but a low fraction found in urine, whereas higher doses resulted in a slower decline in plasma radioactivity and more renal excretion. The publication (John et al. 1961) suggested that after a 15 µg/kg intravenous folic acid dose (similar to the dose of Neocepri),

30-50% of the radioactivity was found in urine the first days after injection, and about half of this was unchanged folic acid. After a rapid initial distribution, the terminal half-life appeared to be >1 hour.

Oral folic acid and folinic acid are not substitutes for intravenous folic acid due to receptor affinity and bioavailability differences relative to intravenously administered folic acid.

No data on special populations or drug-drug interactions are available, which is acceptable considering the well-known safety profile of folic acid.

2.4.5. Conclusions on clinical pharmacology

Literature data indicated that after the intravenous administration of 1 µg per kg of tritiated folic acid to healthy adults, the concentration in the plasma falls very rapidly so that after 3 minutes only 2% of the injected dose/L remains, and by 30 minutes only 0.1 to 0.2 % of the injected dose/L remains.

No *in vivo* human pharmacokinetic interaction studies have been performed with Neocepri. A single dose of 0.5 mg Neocepri would be unlikely to affect the pharmacokinetic behaviour of concomitant medicinal products.

2.5. Clinical efficacy

2.5.1. Dose response study

See main study EC20.1.

2.5.2. Main studies

Study EC20.1

Study EC20.1 was a phase 1, open-label, non-randomised, single dose to assess the safety and biodistribution of ^{99m}Tc-etarfolatide in normal volunteers and ovarian cancer patients.

Methods

The primary objectives of this study were:

1) to determine the biodistribution and excretion of ^{99m}Tc-etarfolatide and estimate the radiation absorbed dose;
2) to evaluate the metabolism and protein binding of ^{99m}Tc-etarfolatide; and
3) to monitor safety parameters following administration of ^{99m}Tc-etarfolatide.

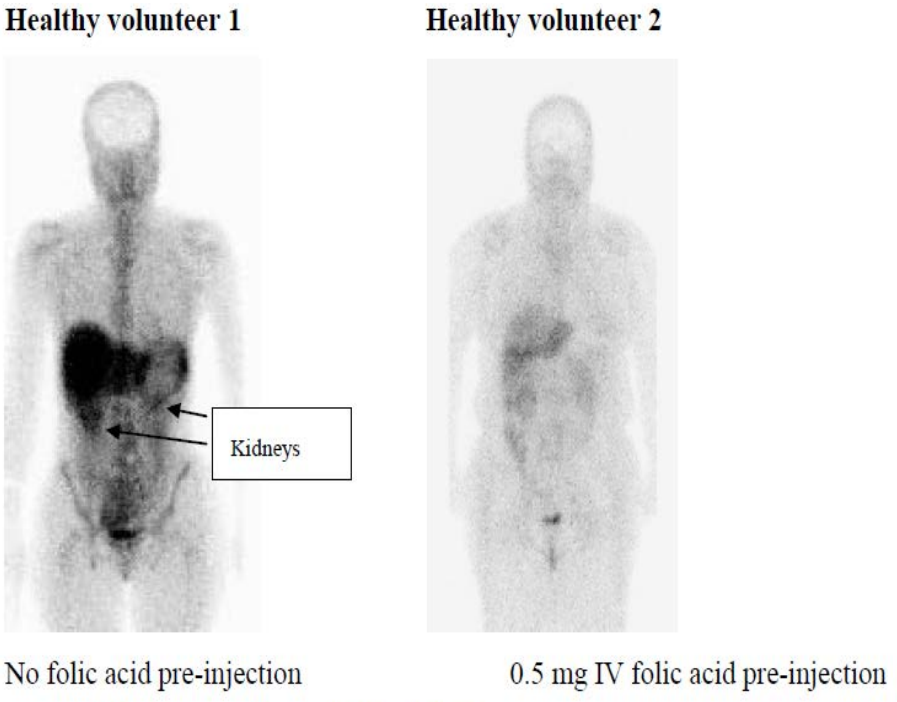
Participants (N=8) received a single injection of etarfolatide labelled with 15 to 20 mCi of ^{99m}Tc. Additionally, 2 of the healthy volunteers and 2 of the patients with known or suspected ovarian cancer received an injection of 0.5 to 2.0 mg of folic acid 1 to 2 minutes before the injection

of ^{99m}Tc-etarfolatide (1 healthy volunteer each received 0.5 mg and 2.0 mg, 1 ovarian cancer patient each received 0.5 mg and 1.0 mg folic acid).

As part of the study, a qualitative assessment by readers of ^{99m}Tc-etarfolatide nuclear scan images with different doses of folic acid was explored. Single Photon Emission Computed Tomography (SPECT) scans were obtained 1-4 hours post ^{99m}Tc-etarfolatide administration.

Results

The Figure below shows the planar images of a healthy volunteer without pre-injection of folic acid compared to a healthy volunteer with a 0.5 mg folic acid pre-injection.



Source: EC20.1 images volunteer #002 and #004

Figure 4: Planar Images Without and With Folic Acid Pre-injection in healthy volunteers

Planar images of an ovarian cancer patient without folic acid pre-injection compared to a patient with 0.5 mg folic acid pre-injection are presented below. The image of patient 2 showed that 0.5 mg pre-injection of folic acid did not block uptake of ^{99m}Tc-etarfolatide in the target lesion.

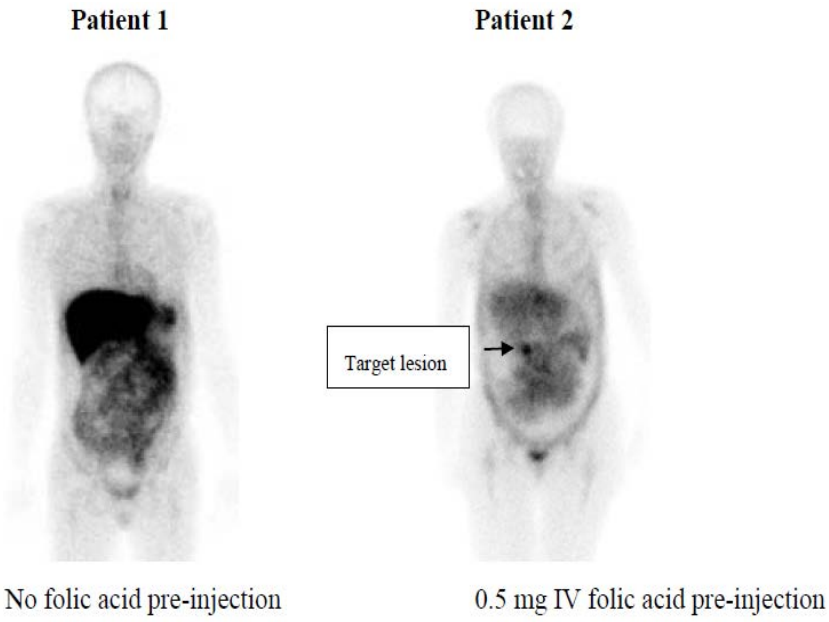


Figure 5: Planar Images With and Without Folic Acid Pre-injection in ovarian cancer patients

Study EC20.11

Study EC20.11 was a phase 1 clinical study to evaluate the biodistribution and safety of ^{99m}Tc-etarfolatide in healthy volunteers (N=20).

Methods

Participants enrolled on study EC20.11 were 18 years of age or older, did not have any major health problems, and provided informed consent prior to enrolment. In addition, participants were excluded if simultaneously participating in another investigative drug or device study, had a known history of chronic abuse of drugs / alcohol, tested positive in pre-study urine drug abuse screen, were taking folic acid supplements, had received another radiopharmaceutical that would interfere with the assessment of the biodistribution of ^{99m}Tc-etarfolatide, or were pregnant / breast-feeding.

All participants first received ^{99m}Tc-etarfolatide SPECT and planar imaging without folic acid. Participants then underwent a second ^{99m}Tc-etarfolatide imaging procedure after being allocated to receive either a 0.5 or 1.0 mg folic acid 1 to 3 minutes pre-injection. The protocol stipulated that the second scan must occur within 4 to 7 days of the first scan in order for an acceptable wash-out period of any residual ^{99m}Tc-etarfolatide.

Objectives of the study were to:

• Determine biodistribution and excretion of the radioactive drug substance (^{99m}Tc-etarfolatide) and estimate the radiation absorbed dose with current dosing parameters.

• Evaluate the safety and tolerability of ^{99m}Tc-etarfolatide in normal volunteers.

• Collect whole-body planar scans and Single Photon Emission Computed Tomography (SPECT) scan of the chest, abdomen, and pelvis to be used for training purposes to show ^{99m}Tc-etarfolatide distribution in normal volunteers.

• Compare SPECT scan of chest, abdomen and pelvis and whole-body planar images with and without injection of folic acid and at different dose levels of folic acid in normal volunteers.

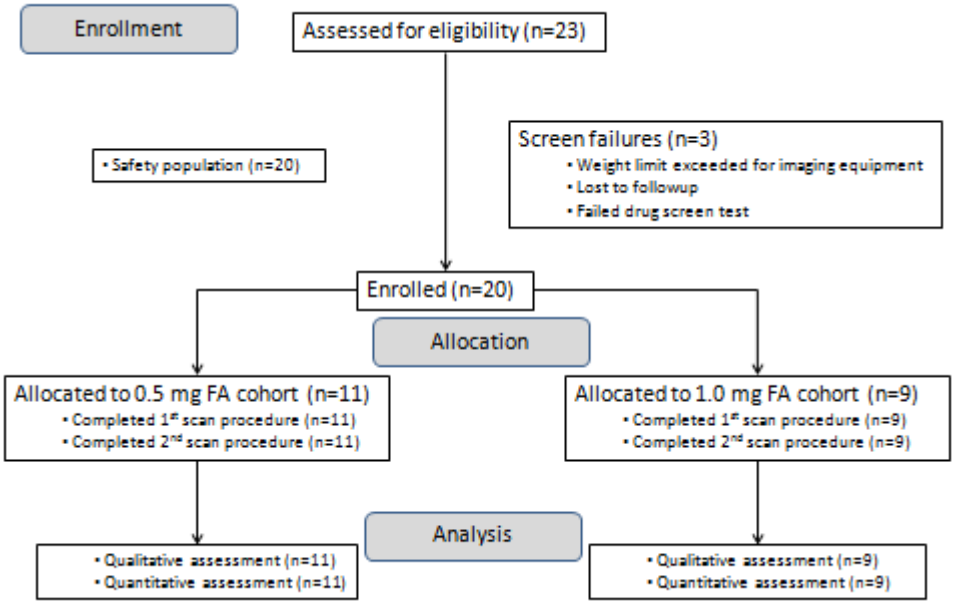
For the Qualitative Image Analysis, two sets of SPECT images for each participant were evaluated by an independent nuclear medicine radiologist blinded to folic acid pre-injection. The blinded nuclear medicine radiologist evaluated each set of images and determined a global assessment of activity/distribution by choosing the image showing the least amount of ^{99m}Tc-etarfolatide background activity/distribution or selecting the option in which both images are equivocal.

For the quantitative assessment, bio-distribution for ^{99m}Tc radio-labelled etarfolatide was determined both with and without folic acid pre-injection based on planar image data.

Results

A total of 23 participants were assessed for eligibility on study EC20.11, with a total of 20 participants receiving study drug and image assessment.

Participants flow



Outcomes and estimation

Qualitative assessment

In 11 out of 11 and 9 out of 9 cases from the 0.5 and 1.0 mg folic acid cohorts, respectively, the blinded independent nuclear medicine radiologist selected the SPECT image associated with folic acid pre-injection as showing lower ^{99m}Tc-etarfolatide activity.

Quantitative assessment

Whole body conjugate planar image data for the 20 patients were obtained using the ^{99m}Tc radio-labelled etarfolatide at approximately 1 hour with and without a folic acid pre-injection. Image data were attenuation corrected using transmission images. Image quantification was based

on the Medical Internal Radiation Dosimetry (MIRD) 16 methodology. Bio-distribution estimates both with and without folic acid pre-injection at one hour post-injection were determined for each subject for Regions of Interest (RoI) of the bone marrow, urinary bladder, intestines, liver, left kidney, and spleen.

Overall, image acquisition was adequate for the purposes of determination of general bio-distribution. Planar images were properly acquired and transferred and image quantification results were consistent and reasonable.

Summary statistics for 0 and 0.5 mg folic acid dose groups are presented in the tables below.

Table 4: Summary statistics for %ID per RoI – no Folic Acid pre-injection

Imaging Region	*N*	*Min.*	*Max.*	*Median*	*Mean (95% CI)*
Bone Marrow	20	10.5%	31.9%	14.54%	17.35% (14.20% - 20.50%)
Urinary Bladder	20	0.4%	3.4%	1.03%	1.34% (0.91% - 1.76%)
Intestines[1]	20	5.0%	12.5%	8.91%	8.86% (7.87% - 9.84%)
Liver including gall bladder	20	14.4%	50.8%	27.23%	27.39% (23.66% - 31.12%)
Left Kidney	20	2.3%	9.7%	4.76%	4.99% (4.24% - 5.75%)
Spleen	20	1.7%	13.7%	4.21%	5.14% (3.69% - 6.60%)

[1] This RoI excludes the liver and kidneys.

Table 5: Summary statistics for %ID per RoI – 0.5 mg Folic Acid pre-injection

Imaging Region	*N*	*Min.*	*Max.*	*Median*	*Mean (95% CI)*
Bone Marrow	11	10.9%	30.5%	17.79%	19.63% (15.90% - 23.35%)
Urinary Bladder	11	1.0%	11.3%	2.72%	3.37% (1.42% - 5.32%)
Intestines[1]	11	4.1%	8.3%	5.84%	6.29% (5.43% - 7.15%)
Liver including gall bladder	11	11.4%	20.7%	15.43%	15.74% (13.66% - 17.82%)
Left Kidney	11	2.0%	4.0%	2.76%	2.87% (2.54% - 3.21%)
Spleen	11	0.6%	3.9%	1.23%	1.57% (0.92% - 2.22%)

[1] This RoI excludes the liver and kidneys.

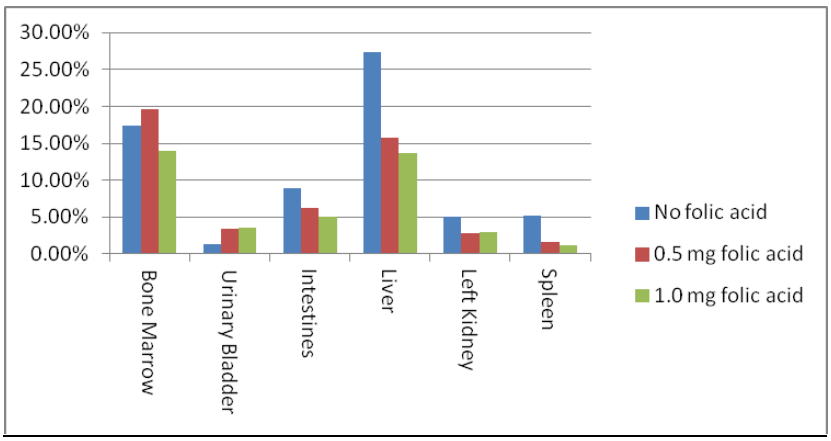


Figure 6: Change in mean ^{99m}Tc-etarfolatide activity for selected organs based on pre-injected folic acid dose level

Table 6: Change in % ^{99m}Tc-etarfolatide injected dose in selected target organs

Imaging Region	no folic acid pre-injection *Mean (95% CI)* n=20	0.5 mg folic acid pre-injection *Mean (95% CI)* n=11

Intestines excluding liver and kidneys	8.86% (7.87% - 9.84%)	6.29% (5.43% - 7.15%)
Liver including gall bladder	27.39% (23.66% - 31.12%)	15.74% (13.66% - 17.82%)
Left kidney	4.99% (4.24% - 5.75%)	2.87% (2.54% - 3.21%)
Spleen	5.14% (3.69% - 6.60%)	1.57% (0.92% - 2.22%)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The dose of 0.5 mg folic acid was chosen for clinical studies based on an optimal balance of tumour to non-tumour background ratio (T:NT) determined in a series of preclinical experiments, along with the objective to select the lowest effective dose of folic acid for administration. The ratio at the 0.5 mg human equivalent dose (HED) of folic acid was improved over that at 1 mg or 2 mg HED in mice (see section 2.3 non-clinical aspects). The non-clinical data submitted as the basis of the dose selection in humans is accepted. The non-clinical estimation is also supported by the results of the study EC20.11 which showed decreased uptake of ^{99m}Tc-etarfolatide in the abdominal organs with the injection of 0.5 mg and 1 mg doses of folic acid.

Overall, on the basis of the pre-clinical evidence, the use of doses above 1 mg would not be advisable, and a lower dose of 0.5 mg dose was chosen to in order to maintain sufficient ^{99m}Tc-etarfolatide binding and visualization of the tumours for lesion characterization assessment of patient FR status, which is considered acceptable.

The clinical study EC20.1 was a small study conducted mainly to evaluate the safety and biodistribution of ^{99m}Tc-etarfolatide in healthy volunteers and ovarian cancer patients. The data pertaining to Neocepri is from four individual subjects and only 2 sets of 2 images were compared without within subject comparisons. These data were complemented with a study conducted in 20 healthy volunteers (EC20.11). Altogether these data are considered sufficient to support the indication claim for Neocepri.

Efficacy data and additional analyses

The quantitative assessment results from study EC20.11 showed that there is a decreased percent injected dose (%ID) in the abdominal normal organs/tissue (intestines, left kidney, liver, spleen) following pre-injection of folic acid, compared to scans without any pre-injection of folic acid. The quantitative assessment results showed a reduced uptake of ^{99m}Tc-etarfolatide in the abdominal normal tissue/organs. Although a study conducted in patients with ovarian cancer with peritoneal deposits would have been more informative and the results presented were obtained in healthy volunteers, some inferences can be drawn for ovarian cancer patients with peritoneal metastases. In patients with tumours that are highly folate receptor positive, the pre-injected folic acid would not be expected to reduce uptake of ^{99m}Tc-etarfolatide in tumour. On the other hand some reduction in ^{99m}Tc-etarfolatide uptake could be expected in tumours that have low folate receptor positivity. Most importantly the provided data showed a decreased uptake in the normal abdominal organs, and thereby supports the claim that Neocepri could enhance the SPECT image quality, by reducing background uptake.

Additional efficacy data needed in the context of a conditional MA

Platinum resistant ovarian cancer is a serious orphan condition and FR expression is a recognised prognostic factor for poor outcome. Due to the poor prognosis in general for platinum resistant

ovarian cancer, there is an unmet medical need in this patient population that could be fulfilled with vintafolide, the proposed therapeutic agent which is to be administered after selection of patients by ^{99m}Tc-etarfolatide imaging. Patients with platinum resistant ovarian cancer have currently limited therapeutic options: topotecan, paclitaxel and pegylated liposomal doxorubicin (PLD). FR(100%) patients represent a small subpopulation of this orphan condition that have a poorer overall prognosis and there are currently no means for patient selection and treatment.

The clinical utility of ^{99m}Tc-etarfolatide after folic acid pre-injection in detecting patients suitable for treatment with vintafolide is based on efficacy data available mainly from one phase 2 study in 38 patients enrolled in the target population and 149 in the mITT population (see EPAR Folcepri). Additional efficacy data is needed in the context of a conditional MA in order to confirm the benefit of vintafolide in combination with PLD in the intended indication (see EPAR Vynfinit), and thus the clinical utility of ^{99m}Tc-etarfolatide and folic acid.

Additional comprehensive clinical data can be provided from study EC-FV-06, a randomised double-blind phase 3 trial comparing vintafolide and PLD in combination versus PLD in patients with PROC. As of the end of October 2013, Study EC-FV-06 had a total of 250 participants randomised, regardless of FR status. Approximately 350 FR(100%) patients will be enrolled in the study. Assuming maximum impact of marketing authorisation on enrolment, it is still estimated that full enrolment of the requisite 350 FR(100%) patients will occur by May 2015 and comprehensive data on efficacy in terms of PFS and OS are likely to be available after conditional approval. The final analysis of the primary endpoint of PFS in FR (100%) patients (245 PFS events) and interim OS analysis is expected to be submitted in December 2015 while the final OS analysis is expected to be available in March 2017 as reflected in the RMP. This study should be conducted by the applicant as a specific obligation for approval.

2.5.4. Conclusions on the clinical efficacy

The benefit of Neocepri in enhancing the SPECT image quality of ^{99m}Tc-etarfolatide, a companion diagnostic to vintafolide is considered sufficiently documented. However, the clinical utility of Neocepri and ^{99m}Tc-etarfolatide are based on the clinical efficacy and safety of vintafolide. The CHMP considers that comprehensive clinical data have not been supplied referring to the safety and efficacy of vintafolide. Therefore, the CHMP considers the following measures necessary to confirm the clinical utility of Neocepri in the context of a conditional MA:

- Submit clinical efficacy results from study EC-FV-06, a randomised double-blind phase 3 trial comparing vintafolide in combination with PLD versus PLD + placebo in patients with platinum-resistant ovarian cancer who express the folate receptor on all target lesions, to further support the clinical utility of a pre-injection of folic acid prior ^{99m}Tc-etarfolatide scan for selection of patients for treatment with vintafolide in combination with PLD.
    - Final clinical study report: March 2017

2.6. Clinical safety

The safety of folic acid was analysed based on data from a literature review covering the last 15 years and including nine clinical studies (including 5 randomised, placebo-controlled and 4 open label studies covering more than 15000 subjects).

Table 7: Tabulations of subjects contributing to the safety analysis

Study and Treatment Groups	Patient Population (N)	FA Dosage (mg/d)	Duration of Treatment
Randomized, Placebo Controlled			
Cole et al 2007 (Colorectal Cancer)			
FA	516	1.0	3–8 years
Placebo	505		
Total	**1021**		
Ebbing et al 2009 (Ischemic Heart Disease)			
FA + 0.4 mg/d vitamin B_{12} + 40 mg/d vitamin B_6	1708	0.8	Median 39 months treatment
FA + 0.4 mg/d vitamin B_{12}	1703	0.8	Median 39 months treatment
Vitamin B_6 alone	1705		
Placebo	1721		
Total	**6837**		
Logan et al 2008 (Colorectal Cancer)			
FA + aspirin	236	0.5	3 years
FA alone	234	0.5	3 years
Aspirin alone	236		
Placebo	233		
Total	**939**		

van Ede et al 2001 (Rheumatoid Arthritis)			
MTX + Placebo	137		
MTX + FA	133	1.0	48 weeks
MTX + Folinic acid	141		
Total	**411**		
Zhang et al 2008 (Cardiovascular Disease)			
FA + vitamin B_6 + vitamin B_{12}	2721	2.5	7.3 years
Placebo	2721		
Total	**5442**		
Open Label			
Ohe et al 2008 (Non-Small Cell Lung Cancer)			
P500	114	0.5	Median number of 21-day treatment courses for both arms was 3 (range, 1–24+)
P1000	111	0.5	
Total	**225**		
Takimoto et al 2007 (Metastatic Cancer)			
HDFA-HPT	28	1.0	Median number of 21-day treatment cycles was 2 (range, 1–16)
HDFA-LPT	34	1.0	Median number of 21-day treatment cycles was 2 (range, 1–8)
MVI-HPT	20	0.35-0.6	Median number of 21-day treatment cycles was 2 (range, 1–15)
MVI-LPT	23	0.35-0.6	Median number of 21-day treatment cycles was 3 (range, 1–17)
Total	**105**		
Scagliotti et al 2003 (Pleural Mesothelioma)			
P+Multivitamin (folic acid, vitamin B12)	43	0.35-1.0	Median number of 21-day treatment cycles was 6 (range, 1–20)
P alone	21		Median number of 21-day treatment cycles was 2 (range, 1–16)
Total	**64**		
Charatcharoenwitthaya et al 2007 (Nonalcoholic Steatohepatitis)			
FA	10	1.0	6 months
Total	**10**		

FA, folic acid; HDFA, high-dose folic acid; HPT, heavily pretreated; LPT, lightly pretreated; MTX, methotrexate; MVI, multivitamin; P, pemetrexed; P500, pemetrexed 500mg/m^2; P1000, pemetrexed 1000 mg/m^2

The 35 papers included in the review covered different aspects such as the safety and efficacy of folic acid supplementation to prevent cardiovascular events or colorectal adenomas/cancer; to reduce toxicity by pemetrexed (predominantly in the treatment of mesothelioma) and by methotrexate (in rheumatoid arthritis); expected adverse events with megadoses of folic acid.

Patient exposure

The population reference intake of folate set by the European Commission's Scientific Committee on Food (SCF) is 200 µg/day orally for adults and 400 µg/day orally during pregnancy (SCF, 1993). In European countries, the average oral folate intake in adults was found to be approximately 300 µg/day in men and 250 µg/day in women (De Bree, 1997). This is similar to the reference intake level, but lower than recommended for pregnant women and women wishing to become pregnant.

The upper limit for daily oral intake of FA has been set at 1000 µg/day by the European Scientific Committee on Food (SCF 2000) as well as by the US Food and Nutrition Board. The bioavailability of oral folic acid varies between 49.3 and 96.7 % (Menke 1994).

The majority of the patients in the literature review (81.6%) had cardiovascular/ischemic heart disease where chronic oral folic acid was administered daily at 0.8-2.5 mg for 3.3-7.3 years to evaluate its effect on decreasing cardiovascular events as well as cancer risk. In one study (van Ede, 2001) patients with rheumatoid arthritis were given 1 mg oral folic acid for 48 weeks (11 months) to evaluate its effect on decreasing the toxicity of methotrexate. Another study (Charatcharoenwitthaya, 2007), patients with non-alcoholic steatohepatitis (NASH) were given 1 mg/day oral folic acid for 6 months to assess the changes in liver biochemical parameters and investigate the presence of possible subclinical folate-deficiency. The remaining studies were on cancer patients treated with pemetrexed with oral folic acid administered at 0.35-1 mg daily to decrease toxicity of pemetrexed.

Adverse events

Allergic events were reported as adverse reactions for 1 mg and 5 mg daily parenteral folic acid administration for the treatment of folic acid deficiency such as megaloblastic anaemia. In overdose cases (more than 15 mg folic acid daily for longer than 4 weeks), the following symptoms have been reported: bitter taste, anorexia, nausea, flatulence, nightmares, excitability and depression.

The occurrence of adverse events (death, bleeding and ulceration, other SAE [including stroke, myocardial infarction, vascular events requiring aspirin, and non-colorectal cancers], and dyspepsia) were non-significant with respect to aspirin and chronic oral folic acid treatment (Logan et al, 2008).

In rheumatoid arthritis, when methotrexate was combined with FA, folinic acid or placebo no significant differences in mucosal adverse effects were noted. On the contrary, liver enzymes were less often increased in the intervention group facilitating a higher mean dose of methotrexate in the intervention group (van Ede et al 2001).

In patients at risk for cardiovascular events, no difference in cancer death or any other cause of death between the active chronic oral folic acid treatment group versus placebo was observed (Zhang et al, 2008).

In patients with a history of colorectal adenomas, chronic (3-year) oral folic acid was associated with a lower incidence of death and colorectal cancer and a higher incidence of non-colorectal cancer. This latter was possibly due to the higher number of prostate cancer cases in the folic acid group compared with the placebo group (Cole et al, 2007).

In cancer patients treated with pemetrexed, the most commonly reported AEs were gastrointestinal and haematological-related and were mild in nature. These toxicities were related to the concurrent

administration of the chemotherapeutic agent pemetrexed (Scagliotti et al, 2003; Takimoto et al, 2007; Ohe et al, 2008). Folic acid supplementation was implemented midway into the overall clinical development program of pemetrexed to decrease the toxicity of pemetrexed.

Post marketing experience

Folic acid as injection is approved in North America for the treatment of megaloblastic anaemia due to deficiency of folic acid as may be seen in tropical or non-tropical sprue, in anaemia of nutritional origin, pregnancy, infancy or childhood. Parenteral administration (intramuscular (IM), intravenous (IV) and subcutaneous (SC) routes) is used if the disease is exceptionally severe or if gastrointestinal absorption is impaired. Doses up to 1 mg daily are used although resistant cases may require larger doses. Allergic sensitization is the only reported adverse reaction following administration of parenteral folic acid (Folic Acid Package Insert from APP Pharmaceuticals).

Folic acid as injection is also approved in other countries including Switzerland, Australia, and in Germany. Approval in Germany is for prophylaxis and therapy of folic acid deficiency in patients where oral folic acid supplementation is not possible or in cases where rapid correction of a severe deficiency is urgently needed. Doses of 5 mg daily by intravenous or intramuscular route are indicated for the treatment of severe folic acid deficiency and administration for prophylaxis is 1-3 times weekly, with isolated reports of allergic reactions reported. In overdose cases (more than 15 mg folic acid daily for longer than 4 weeks), the following symptoms have been reported: bitter taste, anorexia, nausea, flatulence, nightmares, excitability, depression (Folic Acid-Hevert SmPC).

2.6.1. Discussion on clinical safety

A safety analysis based on data from clinical studies conducted was considered not possible due to the small time interval (1-3 minutes) between folic acid and ^{99m}Tc-etarfolatide administrations. The Applicant has conducted a literature review of prophylactic studies with a dose of folic acid in the range of 0.5-2.5 mg given orally. There are no grounds to expect adverse events from parenteral folic acid in the proposed prescribed dose (0.5 mg). In addition, long term possible effects to folic acid are not expected in a population receiving second line therapy for metastatic ovarian cancer.

The only studies describing adverse events were those where vitamin B12 and FA were given to reduce the hematologic toxicity in connection with chemotherapy (pemetrexed). Thus, it is expected that the adverse events were haematological and gastrointestinal and most certainly caused by the chemotherapy and not the vitamin substitution.

A single pre-dose of 0.5 mg (500 µg) of folic acid administered intravenously to cancer patients prior to dosing with ^{99m}Tc-etarfolatide for imaging of ovarian tumours represents only half of the upper limit for daily parenteral dose for the treatment of megaloblastic anaemia, one tenth the recommended parenteral dose for the treatment of severe folic acid deficiency, and half of the upper limit for daily oral intake set in Europe and the US (bioavailability between 49.3% and 96.7%). In clinical trials conducted by the applicant, in which folic acid was given as a slow intravenous push in 554 subjects, no acute allergic reactions were recorded.

The safety of folic acid is well known, and literature data is available to support this. Most of this data is with prolonged administration of folic acid. The proposed use of folic acid in the current application does not require such prolonged periods of administration, and therefore the incidence of most adverse events are expected to be low.

2.6.2. Conclusions on the clinical safety

In view of the available safety data, there are no concerns regarding the clinical safety of the injection of 0.5 mg of folic acid intravenously prior to ^{99m}Tc-etarfolatide scan.

Considering the indication, the route of administration of Neocepri and the close administration of folic acid intravenously and ^{99m}Tc-etarfolatide (1-3 min apart), the CHMP considered that the same PSUR cycle as for etarfolatide should apply.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

PRAC Advice

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Based on the PRAC review of the Risk Management Plan version 3.0, the PRAC considers by consensus that the risk management system for folic acid (Neocepri) in the diagnosis of proposed indications "This medicinal product is for diagnostic use only. Neocepri is administered prior to ^{99m}Tc-etarfolatide, a folate receptor (FR) targeted radiodiagnostic imaging agent for use in ovarian cancer. Neocepri is indicated for the enhancement of ^{99m}Tc-etarfolatide single photon emission computed tomography (SPECT) image quality." is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 8: Summary of the safety concerns

Important identified risks	No important identified risk(s) listed
Important potential risks	Allergic reactions
Missing information	No missing information listed

The PRAC agreed.

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Table 9: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

Allergic reaction	Routine risk minimisation activities: Section 4.8, *Undesirable Effects*, of the SmPC lists allergic reactions as a potential undesirable effect.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Results from two phase 1 studies (EC20.1 and EC20.11) in healthy volunteers and ovarian cancer patients showed that a 0.5 mg injection of Neocepri prior to administration of ^{99m}Tc-etarfolatide significantly reduces the background uptake of ^{99m}Tc-etarfolatide, particularly in the abdomen or pelvic area resulting in better radiotracer visualisation.

Uncertainty in the knowledge about the beneficial effects

Study EC20.11 conducted to support the clinical utility of pre-injection of folic acid was conducted in healthy volunteers, and not in ovarian cancer patients. Therefore, the improvement in diagnostic performance in patients with peritoneal disease as in ovarian cancer needs to be inferred. However, the totality of data combining study EC20.11 with data from study EC20.1 conducted in healthy volunteers and ovarian cancer patients, and the evidence from the phase 2 studies in ovarian cancer patients supporting the clinical utility of ^{99m}Tc-etarfolatide scan after pre-injection of folic acid (see EPAR Folcepri) are considered sufficient to support the claim of improved imaging at the dose selected, 0.5 mg.

Risks

Unfavourable effects

Folic acid is known substance that has been in use for several years. The unfavourable effects are well known, and there are no major safety concerns. At daily doses of 1 or 5 mg by parenteral route (intramuscular, intravenous) there were isolated reports of allergic reactions with manifestations including erythema, pruritus, bronchospasm, nausea or anaphylactic shock.

The proposed use of folic acid in the present application does not require prolonged periods of administration, and therefore the incidence of most adverse events are expected to be low.

Uncertainty in the knowledge about the unfavourable effects

There is no uncertainty in the knowledge about the unfavourable effects.

Benefit-risk balance

Importance of favourable and unfavourable effects

Available clinical data support the claim that Neocepri enhances ^{99m}Tc-etarfolatide single photon emission computed tomography (SPECT) image quality.

The safety of folic acid is known and the benefits of Neocepri are considered to outweigh the minor concerns related to its use.

Benefit-risk balance

Neocepri improves the quality of SPECT imaging with Folcepri. The benefit-risk balance of folic acid intravenous prior ^{99m}Tc-etarfolatide imaging in the proposed indication for the selection of patients for treatment with vintafolide is considered positive.

Discussion on the benefit-risk balance

The clinical utility of ^{99m}Tc-etarfolatide is supported by the results of two phase 1 and one phase 2 comparative study which have shown that patients with FR(100%) benefit from treatment with vintafolide (see EPAR Folcepri). Clinical data on the efficacy of vintafolide and as such clinical utility data on ^{99m}Tc-etarfolatide are currently available mainly from one phase 2 study in 38 patients enrolled in the target population and 149 in the mITT population. Additional efficacy and safety data are needed in the context of a conditional MA in order to confirm the benefit of vintafolide in combination with PLD in the intended indication, and thus the clinical utility of ^{99m}Tc-etarfolatide scan, and the clinical utility of a pre-injection of folic acid, for the detection of patients who would benefit from the treatment. Further clinical efficacy data are expected from the ongoing study EC-FV-06.

The CHMP considered that Neocepri falls under the scope of Article 2 of Commission Regulation (EC) No. 507/2006 as eligible for a Conditional Marketing Authorisation as it belongs to:

a) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

b) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

Furthermore, the requirements listed in Article 4 of the Regulation apply to Neocepri on the basis of the following reasons:

a) The risk-benefit balance of the product is positive:

Folic acid as a pre-injection for ^{99m}Tc-etarfolatide has demonstrated the ability to enhance the images to effectively select patients with the worse prognosis (FR(100%) population), thereby detecting patients who would most likely benefit from vintafolide therapy. Folic acid is well-tolerated and the benefit-risk balance is positive.

b) It is likely that the applicant will be able to provide comprehensive clinical data:

Additional comprehensive clinical efficacy data will be available from study EC-FV-06, a randomised double-blind phase 3 trial comparing vintafolide in combination with PLD versus PLD alone in patients with platinum-resistant ovarian cancer who express the folate receptor on all target lesions as assessed by the ^{99m}Tc-etarfolatide imaging procedure, which will allow to further define the clinical utility of pre-injection of folic acid prior ^{99m}Tc-etarfolatide scan for selection of patients for treatment with the vintafolide in combination with PLD in a larger subset of patients.

c) Fulfilment of unmet medical need in the proposed indications:

Due to the poor prognosis in general for platinum resistant ovarian cancer, there is an unmet medical need in this patient population that could be fulfilled with the proposed medicinal product. Importantly, the subpopulation of women whose disease expresses the FR represents an epidemiologically small subset of PROC with an overall worse prognosis and no approved agents for selection or treatment.

d) The benefits to patients of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

The available data indicate a positive risk-benefit balance for Neocepri for the proposed indication. Given the available results, the timelines of completion of the phase 3 study (EC-FV-06) and in view of the unmet medical need, the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Neocepri in the following indication "This medicinal product is for diagnostic use only. Neocepri is administered prior to ^{99m}Tc-etarfolatide, a folate receptor (FR) targeted radiodiagnostic imaging agent for use in ovarian cancer. Neocepri is indicated for the enhancement of ^{99m}Tc-etarfolatide single photon emission computed tomography (SPECT) image quality." is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Submit clinical efficacy results from study EC-FV-06, a randomised double-blind phase 3 trial comparing vintafolide in combination with PLD versus PLD + placebo in patients with platinum-resistant ovarian cancer who express the folate receptor on all target lesions, to further support the clinical utility of a pre-injection of folic acid prior ^{99m}Tc-etarfolatide scan for selection of patients for treatment with vintafolide in combination with PLD Final clinical study report	March 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.