

**NIHR Innovation Observatory
Evidence Briefing: July 2018****Eflornithine in combination with sulindac for
familial adenomatous polyposis**

NIHRIO (HSRIC) ID: 5685

NICE ID: 9899

LAY SUMMARY

Familial adenomatous polyposis (FAP) is rare condition that can often run in families, but it can also develop in people who do not have a family history of the condition. FAP causes hundreds or thousands of small growths called polyps to develop in the large bowel. These polyps are not cancerous, but if they are not treated some of them are likely to develop into cancer. If there is a family history of FAP, patients will have regular screening from a young age, usually done as a colonoscopy. Polyps usually appear when a person is in their teens if they have classical FAP, and around 10 years later if they have attenuated FAP. For patients with classical FAP, there is a nearly 100% risk of progression to colorectal cancer by 40 years of age if no treatment has been given. The only preventative treatment available for FAP is surgery to remove the colon and sometimes the rectum. After surgery, patients often need to go to the toilet more often, and may need to have a stoma (an opening in the abdomen allowing faeces to be collected in a bag).

Eflornithine in combination with sulindac is being developed as a treatment for FAP. Both these drugs slow down the growth of the polyps in different ways, and taking them together is thought to be potentially more effective than taking them alone. If licensed, this drug combination could reduce or delay the need for surgery or other major endoscopic procedures for people with FAP.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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.

TARGET GROUP

Familial adenomatous polyposis (FAP); (eflornithine in combination with sulindac (CPP-1X/sul))

TECHNOLOGY

DESCRIPTION

CPP-1X/sul is a combination of eflornithine with sulindac.

Eflornithine is a difluoromethylated ornithine compound with antineoplastic activity. Eflornithine irreversibly inhibits ornithine decarboxylase, an enzyme required for polyamine biosynthesis, thereby inhibiting the formation and proliferation of tumour cells. Polyamines are involved in nucleosome oligomerization and DNA conformation, creating a chromatin environment that stimulates neoplastic transformation of cells. This agent has been shown to induce apoptosis in leiomyoma cells.¹ In patients with familial adenomatous polyposis (FAP), ornithine decarboxylase is over-activated and this has been linked with an increase in polyamines which drives the rapid growth of polyp cells. By blocking the enzyme, eflornithine is expected to slow down the cell growth.²

Sulindac is a sulfinylindene derivative prodrug with potential antineoplastic activity. Converted in vivo to an active metabolite, sulindac, a nonsteroidal anti-inflammatory drug (NSAID), blocks cyclic guanosine monophosphate-phosphodiesterase (cGMP-PDE), an enzyme that inhibits the normal apoptosis signal pathway; this inhibition permits the apoptotic signal pathway to proceed unopposed, resulting in apoptotic cell death.³ Sulindac works by activating an enzyme called SSAT that expels polyamines from intestinal cells. This is expected to reduce the levels of polyamine in the intestine, thereby reducing the cell growth and improving the symptoms of the disease.²

The combination of eflornithine and sulindac is under clinical development for the treatment of patients with FAP. In the phase III clinical trial (NCT01483144), participants in the experimental arm are administered 3 x 250mg tablets of eflornithine taken orally once daily, and 1 x 150mg tablet of sulindac taken orally once daily for 24 months.⁴

Eflornithine is licensed in the UK in a cream formulation for the treatment of facial hirsutism in women.⁵

Sulindac is licensed in the UK in tablet formulation for the treatment of pain and inflammation in rheumatic disease and other musculoskeletal disorders, and for acute gout.⁶ As a nonsteroidal anti-inflammatory drug, sulindac is similar in tolerance to naproxen, which has a low incidence of side-effects, but has an intermediate risk of serious upper gastro-intestinal side-effects.⁷

Eflornithine in combination with sulindac does not currently have Marketing Authorisation in the EU for any indication.⁸

Eflornithine in combination with sulindac is in a phase III trial to prevent recurrence of high risk adenomas and second primary colorectal cancers in patients with Stage 0-III colon or rectal cancer.⁹

INNOVATION and/or ADVANTAGES

The combination of eflornithine and sulindac is expected to have an additive effect, slowing down the growth of the polyps more than either substance alone.² If licensed, it will offer an additional treatment option for patients with FAP, who currently have no effective therapy other than surgery or major endoscopic procedures intended to prevent or delay the progression of polyps into high risk adenomas and ultimately into cancers.²

DEVELOPER

Cancer Prevention Pharmaceuticals, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

CPP-1X/sul was designated an orphan drug in the EU for FAP in January 2013.¹⁰

CPP-1X/sul was designated an orphan drug in the USA for FAP in January 2013.¹¹

CPP-1X/sul was granted Fast Track designation by FDA for FAP in September 2017.¹²

PATIENT GROUP

BACKGROUND

Familial adenomatous polyposis (FAP) is an autosomal-dominant condition caused by germline adenomatous polyposis coli (APC) gene mutations.¹³ The condition can be hereditary, although around 1 in 4 people with FAP do not have a family history of the condition.¹⁴ Patients with classical FAP have hundreds to thousands of colorectal adenomas (neoplastic polyps), whilst the attenuated form leads to the formation of fewer than 100 polyps.¹³ In classical FAP the polyps usually start to appear when a person is in their teens, whilst in attenuated FAP the polyps appear approximately 10 years later.¹⁴

Hundreds of polyps can develop in a patient's bowel in the absence of any symptoms. If the polyps are not treated symptoms may appear, however, some people remain asymptomatic until a polyp has developed into a cancer. FAP and bowel cancer share certain symptoms such as blood or mucus in the stools, diarrhoea or constipation, pain in the abdomen or rectum, and weight loss for no obvious reason.¹⁴ Other symptoms of FAP include polyps along other sections of the gut, skin and bone cysts and congenital hypertrophy of the retinal pigment epithelium (CHRPEs) (dots at the back of the eye).¹⁵

A genetic blood test can determine the presence of the altered FAP gene, and the test is usually offered from the age of 12 to 14 years. After diagnosis with FAP, regular (annual) bowel checks are needed,¹⁵ and an oesophagogastroduodenoscopy (OGD) is done from the age of around 25 years every 1 to 5 years to check the upper gastrointestinal tract, as most people with FAP develop polyps in the duodenum.¹⁴ Depending on how the polyps look and the total number of polyps, the clinician may recommend to continue with screening, or to have an operation to remove the large bowel.¹⁵ Generally, surgery is performed between the ages of 16 and 20 years, and for older patients presenting with symptoms surgery is usually carried out as soon as possible.¹⁶ Patients with classical FAP have a nearly 100% risk for colorectal cancer by 40 years of age if prophylactic colectomy is not performed, and 80% of attenuated FAP patients will have colorectal cancer by 60 years of age in the absence of either total colectomy or endoscopic polyp clearance.¹³

The majority of FAP patients present with extra-colonic manifestations (ECM) later in life, including cutaneous lesions, desmoids tumours and upper-gastrointestinal polyps. The duodenum is the second most common site of polyp development in patients with FAP, and duodenal adenomas tend to occur approximately 15 years after the appearance of colonic adenomas, with a lifetime risk approaching 100% and cumulative incidence rates of Spigelman stage IV disease and carcinoma at 4% to 10%.¹⁷

CLINICAL NEED and BURDEN OF DISEASE

The estimated prevalence in FAP ranges from around 3 persons per 100,000¹⁸ to 6 persons per 100,000.¹⁹ Using the latest mid-year population estimated for England and Wales (2016), this would equate to between 1,751 and 3,503 persons.²⁰

It is estimated that 1% of bowel cancers are linked to FAP.¹⁴ There were 23,485 registrations of newly diagnosed cases of malignant neoplasm of colon (ICD-10 code C18) in England in 2016, which would equate to around 235 cases linked to FAP.²¹

FAP can be difficult to cope with, due to the uncertainty of not knowing if cancer could develop, and the need for complicated decisions about when to have surgery. As the condition is often inherited it can impact on a person's life from childhood. Patients need to undergo lifetime surveillance, and multiple surgical and endoscopic procedures. Following initial surgery, patients usually have issues associated with frequent bowel movement and increases in urgency/incontinence. In some cases patients will require a stoma.¹⁴ After this surgery patients continue to need endoscopic surveillance, and may require further surgery. This can have a significant effect on quality of life for patients and their families. Life expectancy in patients with FAP is less than that of the general population.¹⁶

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas (CG118). March 2011.
- NICE interventional procedure guidance. Endoscopic full thickness removal of non-lifting colonic polyps (IPG580). May 2017.
- NICE interventional procedure guidance. Combined endoscopic and laparoscopic removal of colonic polyps (IPG503). September 2014.
- NICE diagnostic guidance. Virtual chromoendoscopy to assess colorectal polyps during colonoscopy (DG28). May 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Pancreatic (Adult). A02/S/b.
- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.

OTHER GUIDANCE

- American Society of Colon and Rectal Surgeons. Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes. 2017.²²
- American College of Gastroenterology. Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. February 2015.²³
- European Society for Medical Oncology. ESMO Clinical Guidelines for Familial Risk-Colorectal Cancer. June 2013.²⁴

CURRENT TREATMENT OPTIONS

The only current prophylactic treatment option for patients with FAP and an intact large bowel is surgery. The simplest operation is an ileo-rectal anastomosis, which involves removing the colon and attaching the small intestine to the rectum. After this operation regular screening is required as adenomas may develop in the rectum, which may require further surgery several years later.¹⁵

A larger procedure is a pouch operation, when the colon and rectum are removed and a portion of the small bowel is used to make a pouch that can store faeces and function like an artificial rectum. One operation creates a temporary arrangement where the end of the small bowel is brought out through the abdominal wall. Once the pouch has healed a second operation is needed to rejoin the pouch to the upper bowel. This procedure removes more bowel and therefore screening of the rectum is not required afterwards.¹⁵ However, 50% of such patients develop adenomas in the pouch, and require surveillance and procedures similar to those patients with a retained rectum. Progressive polyposis or development of advanced adenomas in the rectum of pouch requires major excisional or surgical procedures.^a

A third option is a pan-proctocolectomy and ileostomy. This involves the removal of the colon and the rectum; the end of the small bowel is brought to the skin surface of the abdomen (stoma) and faeces are collected in a disposable bag. This operation means there is no large bowel left that is at risk from polyps.¹⁵

EFFICACY and SAFETY

Trial	NCT01483144 , EudraCT 2012-000427-41, CPP-FAP-310; CPP-1X/sul vs eflornithine with placebo vs sulindac with placebo; phase III
Sponsor	Cancer Prevention Pharmaceuticals, Inc.
Status	Ongoing
Source of Information	Trial Registry ⁴
Location	5 EU countries (incl UK), USA and Canada
Design	Randomised, double-blind, active-controlled
Participants	n=171; aged 18 yrs and older; diagnosis of phenotypic classical FAP with disease involvement of the duodenum and/or colon/rectum/pouch

^a Information supplied by company.

Schedule	Randomised to 3 x 250mg tablets of eflornithine taken orally once daily, and 1 x 150mg tablet of sulindac taken orally once daily; 3 x 250mg tablets of eflornithine taken orally once daily, and 1 x placebo tablet taken orally once daily or 1 x 150mg tablet of sulindac taken orally once daily and 3 x placebo tablets taken orally once daily.
Follow-up	Active treatment period 24-48 mths, follow-up 1 mth
Primary Outcomes	<ul style="list-style-type: none"> • Delaying time to the first occurrence of any FAP-related event [Time Frame: Up to 48 mths from the start of treatment]
Secondary Outcomes	<ul style="list-style-type: none"> • Presence or absence of an ornithine decarboxylase (ODC) polymorphism [Time Frame: Up to 48 mths from the start of treatment] • Excretion of 4 urinary polyamines [Time Frame: Up to 48 mths from the start of treatment] • Analysis of adverse events and clinical laboratory abnormalities indicating possible adverse events [Time Frame: Up to 48 mths from the start of treatment] • Pharmacokinetics (AUC, Cmax, Cmin, tmax, Css, CL) of study medication [Time Frame: pre-dose and 1, 2, 4, and 8 hours post-dose (5 time points at month 3)] • Evaluate polyamine levels [Time Frame: Up to 48 mths from the start of treatment] • Pt reported quality of life will be evaluated using health related quality of life questionnaires and pt utilities [Time Frame: Up to 48 mths from the start of treatment] • Evaluation of the time to the first FAP-related beneficent event [Time Frame: Up to 48 mths from the start of treatment]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as April 2019.

ESTIMATED COST and IMPACT

COST

The cost of CPP-1X/sul is not yet known.

Sulindac is already marketed in the UK for the treatment of pain and inflammation in rheumatic disease and other musculoskeletal disorders, and for acute gout: a pack of 56 x 100mg tablets has a drug tariff price of £29.78, and a pack of 56 x 200mg tablets has a drug tariff price of £38.29.⁶

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: improved quality of life by not having surgery, reduced time off school/work | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input checked="" type="checkbox"/> Other: possible decrease in need for surgery, possible short-term increase in need for surveillance, possible long-term decrease in need for surveillance | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input checked="" type="checkbox"/> Other: reduced need for surgical intervention and ongoing care (particularly stoma care), but cost of product unknown; reduction in cost due to fewer hospital visits, surveillance and surgical procedures | <input type="checkbox"/> None identified |

OTHER ISSUES

- Clinical uncertainty or other research question identified
- None identified

REFERENCES

- ¹ National Cancer Institute. *NCIthesaurus: Eflornithine (Code C226)*. Available from: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&version=18.05d&ns=ncit&code=C226&key=n681394960&b=1&n=null [Accessed 25th June 2018]
- ² European Medicines Agency. *Eflornithine in combination with sulindac for the treatment of familial adenomatous polyposis*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2013/03/WC500139533.pdf [Accessed 25th June 2018]
- ³ National Cancer Institute. *NCIthesaurus: Sulindac (Code C850)*. Available from: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&version=18.05d&ns=ncit&code=C850&key=525023877&b=1&n=null [Accessed 25th June 2018]
- ⁴ ClinicalTrials.gov. *Trial of Eflornithine Plus Sulindac in Patients With Familial Adenomatous Polyposis (FAP): NCT01483144*. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01483144> [Accessed 25th June 2018]
- ⁵ British National Formulary. *Eflornithine*. Available from: <https://bnf.nice.org.uk/drug/eflornithine.html> [Accessed 25th June 2018]
- ⁶ British National Formulary. *Sulindac*. Available from: <https://bnf.nice.org.uk/drug/sulindac.html> [Accessed 25th June 2018]
- ⁷ British National Formulary. *Non-steroidal anti-inflammatory drugs*. Available from: <https://bnf.nice.org.uk/treatment-summary/non-steroidal-anti-inflammatory-drugs.html> [Accessed 25th June 2018]
- ⁸ British National Formulary. *Search results*. Available from: [https://bnf.nice.org.uk/drug/sulindac.html#Search?q=eflornithine sulindac](https://bnf.nice.org.uk/drug/sulindac.html#Search?q=eflornithine%20sulindac) [Accessed 25th June 2018]
- ⁹ ClinicalTrials.gov. *S0820, Adenoma and Second Primary Prevention Trial (PACES): NCT01349881*. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01349881> [Accessed 25th June 2018]
- ¹⁰ European Medicines Agency. *EU/3/12/1086*. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2013/03/human_orphan_001162.jsp&mid=WC0b01ac058001d12b [Accessed 25th June 2018]
- ¹¹ US Food & Drug Administration. *Search Orphan Drug Designations and Approvals*. Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/oodp/detailedIndex.cfm?cfgridkey=387012> [Accessed 25th June 2018]
- ¹² BioSpace. *FDA Grants "Fast Track" Status To Cancer Prevention Pharmaceuticals' Lead Drug CPP-1X/Sul For Treatment Of Familial Adenomatous Polyposis*. 18 September 2017. Available from: <https://www.biospace.com/article/releases/fda-grants-fast-track-status-to-b-cancer-prevention-pharmaceuticals-b-lead-drug-cpp-1x-sul-for-treatment-of-familial-adenomatous-polyposis-/?keywords=eflornithine> [Accessed 25th June 2018]
- ¹³ Ternent CA, Thorson AG. *Familial adenomatous polyposis syndromes*. *BMJ Best Practice*. Available from: <https://bestpractice.bmj.com/topics/en-gb/652> [Accessed 25th June 2018]
- ¹⁴ Macmillan Cancer Support. *Familial Adenomatous Polyposis (FAP)*. Available from: <https://www.macmillan.org.uk/information-and-support/diagnosing/causes-and-risk-factors/genetic-testing-and-counselling/fap.html#20305> [Accessed 25th June 2018]
- ¹⁵ University Hospital Southampton NHS Foundation Trust. *Familial adenomatous polyposis (FAP)*. May 2016. Available from: <http://www.uhs.nhs.uk/Media/ControlledDocuments/PatientInformation/Genetics/Familial-Adenomatous-Polyposis-FAP-leaflet.pdf> [Accessed 25th June 2018]
- ¹⁶ Tudyka VN, Clark SK. *Surgical treatment in familial adenomatous polyposis*. *Ann Gastroenterol*. 2012; 25(3): 201-206. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959379/> [Accessed 30th July 2018]

-
- ¹⁷ Campos FG, Sulbaran M, Safatle-Ribeiro AV, Real Martinez CA. Duodenal adenoma surveillance in patients with familial adenomatous polyposis. *World J Gastrointest Endosc.* 2015 Aug 10; 7(10): 950-959. Available from: <http://doi.org/10.4253/wjge.v7.i10.950>
- ¹⁸ Genomics Education Programme. *Familial Adenomatous Polyposis*. Available from: <https://www.genomicseducation.hee.nhs.uk/resources/genetic-conditions-factsheets/item/76-familial-adenomatous-polyposis/> [Accessed 2nd July 2018]
- ¹⁹ Orphanet. *Prevalence and incidence of rare diseases: Bibliographic data*. June 2018. Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed 25th June 2018]
- ²⁰ Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2016#main-points> [Downloaded 24th November 2018] [Accessed 25th June 2018]
- ²¹ Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Downloaded 6th February 2018] [Accessed 25th June 2018]
- ²² Herzig D, Hardimann K, Weiser M, Yu N, Paquette I, Feingold DL et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes. *Diseases of the Colon & Rectum.* 2017; 60:881-894. Available from: <http://doi.org/10.1097/DCR.0000000000000912>
- ²³ Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. *American Journal of Gastroenterology.* 2015; 110:223-262. Available from: <http://doi.org/10.1038/ajg.2014.435>
- ²⁴ Balmaña J, Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. *Annals of Oncology.* 2013; 24(6): vi73-vi80. Available from: <http://doi.org/10.1093/annonc/mdt209>