Pemigatinib

Indication
Locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy.

Regimen details
Pemigatinib 13.5mg once daily for 14 days followed by 7 days off therapy

Cycle frequency
Every 3 weeks

Number of cycles
Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity

Administration
The tablets should be taken at approximately the same time every day. Patients should not crush, chew, split or dissolve the tablets. Pemigatinib may be taken with or without food

If a dose of pemigatinib is missed by 4 or more hours or vomiting occurs after taking a dose, an additional dose should not be administered and dosing should be resumed with the next scheduled dose

Pre-medication
N/A

Emetogenicity
Nausea is common

Additional supportive medication
Supply metoclopramide and loperamide with first cycle

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Bone profile	14 days
Opthalmological examination including OCT	Baseline

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST), bone profile
Ophthalmological examination (including OCT) should be performed prior to initiation of therapy and every 2 months for the first 6 months of treatment and then every 3 months thereafter, and urgently at any time for visual symptoms – refer to LTH ophthalmology department.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN
Phosphate	>1.78 - ≤ 2.26mmol/L

Dose modifications

Concomitant use of pemigatinib with strong CYP3A4 inhibitors

Concurrent use of strong CYP3A4 inhibitors, including grapefruit juice, should be avoided during treatment with pemigatinib. If co-administration with a strong CYP3A4 inhibitor is necessary, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily

Hyperphosphataemia:

Adverse reaction	pemigatinib dose modification
>1.78 - ≤ 2.26mmol / L	• pemigatinib should be continued at current dose and low phosphate diet initiated. (see appendix 1)
>2.26 - ≤ 3.23mmol/L	• pemigatinib should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly, dose of phosphate lowering therapy should be adjusted as needed until level returns to <2.26mmol/L. (see trust policy http://lthtr-documents/current/P645.pdf) • pemigatinib should be withheld if levels do not return to <2.26mmol/L within 2 weeks of starting a phosphate lowering therapy*. pemigatinib and phosphate-lowering therapy should be restarted at the same dose when level returns to <2.26mmol/L • Upon recurrence of serum phosphate at > 2.26mmol/L with phosphate-lowering therapy, pemigatinib should be reduced 1 dose level.
>3.23mmol/L	• pemigatinib should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly and dose of phosphate lowering therapy should be adjusted as needed until level returns to <2.26mmol/L. • pemigatinib should be withheld if levels continue >3.23mmol/L for 1 week. pemigatinib and phosphate-lowering therapy should be restarted 1 dose level lower when serum phosphate is <2.26mmol/L. • If there is recurrence of serum phosphate >3.23mmol/L following 2 dose reductions, pemigatinib should be permanently discontinued.

*e.g calcium acetate (RENACET) 475mg **with** meals, titrate as needed

Renal impairment

Dose adjustment is not required for patients with mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis. For patients with severe renal impairment, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily

Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function. Within the first cycle, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Hepatic impairment

Dose adjustment is not required for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily

Serous retinal detachment:

Adverse reaction	**pemigatinib dose modification**
Asymptomatic	• pemigatinib should be continued at current dose. Monitoring should be performed as described in section 4.4.
Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib should be resumed at the next lower dose level. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	• pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.

Adverse effects –

for full details consult product literature/ reference texts

Hyponatraemia
Hyperphosphataemia
Hypophosphataemia
Dysgeusia
Dry eyes
Serous retinal detachment
Nausea
Stomatitis
Diarrhoea
Hand and foot syndrome
Nail toxicity
Arthralgia
Fatigue
Increased blood creatinine

Significant drug interactions

– for full details consult product literature/ reference texts

Where possible, concurrent use of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, ritonavir) should be avoided during treatment with pemigatinib (see above regarding dose modification)

Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with pemigatinib. Concomitant use of pemigatinib with St John's wort is contra-indicated

PPIs should be avoided in patients receiving pemigatinib

Co-administration of pemigatinib with CYP2B6 substrates (e.g. cyclophosphamide, ifosfamide, methadone, efavirenz) may decrease their exposure. Close clinical surveillance is recommended when pemigatinib is administered with these medicinal products

Co-administration of pemigatinib with P-gp substrates (e.g. digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. Pemigatinib administration should be separated by at least 6 hours before or after administration of P-gp substrates with a narrow therapeutic index

Additional comments

References

https://www.medicines.org.uk/emc/product/12485/smpc#gref

Iheagwara, OS et al. Phosphorus, phosphorous and phosphate. *Hemodialysis International* 2013; 17:479–482.

LTH Guideline for the Management of Mineral and Bone Disorders in Dialysis Patients
http://lthtr-documents/current/P645.pdf

Appendix 1

Low Phosphate Diet
OCT 2017.docx

THIS PROTOCOL HAS BEEN DIRECTED BY Dr C Mitchell, DESIGNATED LEAD CLINICIAN FOR

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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