7 Targeted therapy responsive malignancy

ANTINEOPLASTIC DRUGS › PROTEASOME INHIBITORS

Bortezomib 03-Nov-2020

I DRUG ACTION Bortezomib is a proteasome inhibitor.

I INDICATIONS AND DOSE

Multiple myeloma (specialist use only) | Mantle cell lymphoma (specialist use only)

▶ BY INTRAVENOUS INJECTION, OR BY SUBCUTANEOUS INJECTION

▶ Adult: (consult product literature or local protocols)

IMPORTANT SAFETY INFORMATION

Bortezomib injection is for intravenous or subcutaneous administration only. Inadvertent intrathecal administration with fatal outcome has been reported.

I CONTRA-INDICATIONS Acute diffuse infiltrative pulmonary disease . pericardial disease

I CAUTIONS Amyloidosis . cardiovascular disease . consider antiviral prophylaxis for herpes zoster infection . dehydration . diabetes (may affect blood glucose) . history of syncope . pulmonary disease . risk factors for seizures . risk of neuropathy—consult product literature

I INTERACTIONS → Appendix 1: bortezomib

I SIDE-EFFECTS

▶ Common or very common Anaemia . anxiety . appetite abnormal . arrhythmias . asthenia . chills . constipation . cough . decreased leucocytes . diabetes mellitus . diarrhoea . dizziness . dysphagia . dyspnoea . electrolyte imbalance . encephalopathy . enzyme abnormality . eye inflammation . fever . fluid imbalance . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . hair disorder . headaches . hearing impairment . heart failure . hepatic disorders . hiccups . hyperbilirubinaemia . hypersensitivity . hypertension . hypotension . increased risk of infection . ischaemic heart disease . lethargy . loss of consciousness . malaise . mood altered . muscle complaints . muscle weakness . nausea . nerve disorders . neuromuscular dysfunction . neutropenia . oedema . oral disorders . oropharyngeal complaints . pain . renal impairment . sensation abnormal . sepsis . skin reactions . sleep disorder . syncope . taste altered . thrombocytopenia . tinnitus . ventricular dysfunction . vertigo . vision disorders . vomiting . weight changes

▶ Uncommon Altered smell sensation . angioedema . antibiotic associated colitis . arthritis . azotaemia . cardiac arrest . cardiomyopathy . cardiovascular disorder . cerebrovascular insufficiency . chest discomfort . circulation impaired . circulatory collapse . coagulation disorders . concentration impaired . confusion . Cushing's syndrome . dry eye . dysphonia . ear discomfort . embolism and thrombosis . eye discomfort . eye disorders . failure to thrive . gait abnormal . gas exchange abnormal . genital pain . haemolytic anaemia . hallucination . hyperthyroidism . increased leucocytes . injury . irritable bowel syndrome . joint disorders . lymphadenopathy . memory loss . movement disorders . mucous membrane disorder . myopathy . neurotoxicity . palpitations . pancreatitis . pancytopenia . pericardial disorders . pericarditis . posterior reversible encephalopathy syndrome (PRES) (discontinue) . proteinuria . psychiatric disorders . psychotic disorder . pulmonary hypertension . pulmonary oedema . reflexes abnormal . respiratory disorders . rhinorrhoea . seizure . sensation of pressure . severe cutaneous adverse reactions (SCARs) . sexual dysfunction . shock . SIADH . skin mass . skin ulcers .

speech disorder . sweat changes . temperature sensation altered . thirst change . tremor . tumour lysis syndrome . urinary disorders . urinary tract disorder . vascular disorders . vasculitis . vasodilation

▶ Rare or very rare Acidosis . acute coronary syndrome . alcohol intolerance . amyloidosis . apnoea . ascites . atrioventricular block . bladder irritation . blood disorders . bone disorder . bone fracture . brain oedema . breast disorder . cardiac valve disorder . cholelithiasis . CNS haemorrhage . cognitive disorder . coma . coronary artery insufficiency . delirium . drooling . ear disorder . erythromelalgia . fistula . gout . healing impaired . hypothyroidism . inflammation . lymphoedema . macrophage activation . mass . meningitis . metabolic disorder . multi organ failure . nail disorder . neoplasm malignant . neoplasms . nervous system disorder . paralysis . paresis . pelvic pain . perforation . photosensitivity reaction . platelet abnormalities . procedural complications . prostatitis . radiation injury . seborrhoea . sudden death . suicidal ideation . testicular disorders . throat complaints . ulcer . vaginal ulceration . venous insufficiency . vitamin deficiencies

▶ Frequency not known Herpes zoster reactivation . JC virus infection . progressive multifocal leukoencephalopathy (PML)

ı CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

ı PREGNANCY Toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment–monitor for toxicity. Dose adjustments Manufacturer advises reduce dose in moderate to severe impairment—consult product literature.

ı RENAL IMPAIRMENT No information available for creatinine clearance less than 20 mL/minute/1.73m2.

ı MONITORING REQUIREMENTS

▶ Monitor blood-glucose concentration in patients on oral antidiabetics.

▶ Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological signs or symptoms)—discontinue treatment if diagnosed.

▶ Chest x-ray recommended before treatment to monitor for pulmonary disease—discontinue if interstitial lung disease develops.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Bortezomib for previously untreated mantle cell lymphoma (December 2015) NICE TA370 Recommended

▶ Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (April 2014) NICE TA311 Recommended

▶ Bortezomib and thalidomide for the first-line treatment of multiple myeloma (July 2011) NICE TA228 Recommended with restrictions

▶ Bortezomib monotherapy for relapsed multiple myeloma (October 2007) NICE TA129 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Bortezomib (Velcade ®) in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation

(January 2014) SMC No. 927/13 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for injection

▶ Bortezomib (Non-proprietary)
Bortezomib 2.5 mg per 1 ml Bortezomib 3.5mg/1.4ml solution for injection vials | 1 vialP £495.55 (Hospital only)
Powder for solution for injection
▶ Bortezomib (Non-proprietary)
Bortezomib 1 mg Bortezomib 1mg powder for solution for injection vials | 1 vialP £217.82 (Hospital only)
Bortezomib 2.5 mg Bortezomib 2.5mg powder for solution for injection vials | 1 vialP £544.56 (Hospital only)
Bortezomib 3.5 mg Bortezomib 3.5mg powder for solution for injection vials | 1 vialP £533.67–£762.38 (Hospital only)
▶ Velcade (Janssen-Cilag Ltd)
Bortezomib 3.5 mg Velcade 3.5mg powder for solution for injection vials | 1 vialP £762.38 (Hospital only)

Carfilzomib 15-Dec-2021

I DRUG ACTION Carfilzomib is an irreversible selective proteasome inhibitor that disrupts tumour cell turnover and induces apoptosis.

I INDICATIONS AND DOSE

Multiple myeloma (specialist use only)

▶ BY INTRAVENOUS INFUSION

▶ Adult: (consult product literature or local protocols)

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: CARFILZOMIB (KYPROLIS ▪): REMINDER OF RISK OF POTENTIALLY FATAL CARDIAC EVENTS (AUGUST 2019)

Cases of cardiac arrest, cardiac failure, and myocardial infarction, including fatalities, have been reported in patients with or without pre-existing cardiac disorders receiving carfilzomib. Healthcare professionals are advised to monitor patients for signs and symptoms of cardiac disorders before and during carfilzomib treatment. Carfilzomib should be discontinued if severe or life-threatening cardiac events occur; restarting treatment may be considered at a lower dose once the condition is controlled and the patient is stable.

MHRA/CHM ADVICE: CARFILZOMIB (KYPROLIS ▪): RISK OF REACTIVATION OF HEPATITIS B VIRUS (NOVEMBER 2019)

An EU review of worldwide data has identified reports of hepatitis B virus (HBV) reactivation in patients treated with carfilzomib. Healthcare professionals are advised to screen all patients for HBV before initiating treatment; those with unknown serology already being treated with carfilzomib should also be screened. Patients with positive serology should be considered for antiviral prophylaxis, and be monitored for signs of HBV reactivation during and after treatment; immediate medical attention should be sought if signs and symptoms of HBV reactivation develop. Experts should be consulted for advice about HBV treatment and the continuation, interruption, or resumption of carfilzomib in patients with HBV reactivation.

I CAUTIONS Elderly (over 75 years)—higher incidence of adverse effects . ensure adequate hydration . hepatitis B carriers (consider antiviral prophylaxis) . infusion-related reactions . recent history of myocardial infarction . risk factors for thromboembolism . risk of cardiac failure . risk of herpes zoster reactivation . uncontrolled angina . uncontrolled arrhythmias

CAUTIONS, FURTHER INFORMATION

▶ Infusion-related reactions gPremedication with dexamethasone advised to reduce incidence and severity of infusion-related reactions. M

▶ Risk of herpes zoster reactivation gConsider antiviral prophylaxis for herpes zoster infection. M

▶ Hepatitis B reactivation gHepatitis B reactivation has been reported in patients taking carfilzomib. Patients with positive hepatitis B serology should be considered for prophylactic antiviral therapy, and closely monitored for clinical and laboratory signs of active hepatitis B infection during and after treatment. Experts in the treatment of hepatitis B infection should be consulted as necessary. M

I INTERACTIONS → Appendix 1: carfilzomib

I SIDE-EFFECTS

▶ Common or very common Anaemia . anxiety . appetite decreased . arrhythmias . arthralgia . asthenia . cataract . chest pain . chills . confusion . constipation . cough . decreased leucocytes . dehydration . diarrhoea . dizziness . dysphonia . dyspnoea . electrolyte imbalance . embolism and thrombosis . fever . flushing . gastrointestinal discomfort . haemorrhage . headache . heart failure . hyperbilirubinaemia . hyperglycaemia . hyperhidrosis . hypertension . hyperuricaemia . hypoalbuminaemia .

hypotension . increased risk of infection . influenza like illness . infusion related reaction . insomnia . malaise . muscle complaints . muscle weakness . myocardial infarction . nausea . neutropenia . oropharyngeal pain . pain . palpitations . peripheral neuropathy . peripheral oedema . pulmonary hypertension . pulmonary oedema . renal impairment . respiratory disorders . sensation abnormal . sepsis . skin reactions . thrombocytopenia . tinnitus . toothache . vision blurred . vomiting

▶ Uncommon Cardiac arrest . cardiomyopathy . Clostridioides difficile colitis . gastrointestinal perforation . haemolytic uraemic syndrome . hepatic disorders . hepatitis B reactivation . intracranial haemorrhage . multiple organ dysfunction syndrome . myocardial ischaemia . pericardial effusion . pericarditis . stroke . tumour lysis syndrome

▶ Rare or very rare Angioedema . posterior reversible encephalopathy syndrome (PRES) . thrombotic microangiopathy

▶ Frequency not known Progressive multifocal leukoencephalopathy (PML) .QT interval prolongation

CONCEPTION AND CONTRACEPTION Manufacturer recommends effective contraception during and for 1 month after treatment in women of childbearing potential; hormonal contraceptives associated with a risk of thrombosis should be avoided. Male patients should use effective contraception during and for 3 months after treatment if their partner is pregnant or of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid during and for at least 2 days after treatment—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution (increased risk of side-effects), particularly in moderate to severe impairment (limited information available).

RENAL IMPAIRMENT Manufacturer advises caution—increased incidence of adverse effects.

PRE-TREATMENT SCREENING gPatients should be screened for hepatitis B before treatment. M

MONITORING REQUIREMENTS gMonitor the following patient parameters: serum potassium concentration at least monthly; signs and symptoms of fluid overload,

especially in those at risk of cardiac failure; renal function at treatment initiation and at least monthly during treatment—consider dose modification; hepatic function at treatment initiation and monthly during treatment—consider dose modification; platelet count; blood pressure at treatment initiation and regularly during treatment. Also monitor for signs and symptoms of thrombotic microangiopathy, tumour lysis syndrome and progressive multifocal leukoencephalopathy—withhold treatment if suspected. M

HANDLING AND STORAGE Manufacturer advises store in a refrigerator at 2–8°C.

PATIENT AND CARER ADVICE Manufacturer advises that patients and carers are warned to report signs and symptoms of thromboembolism (such as dyspnoea, chest pain, arm or leg swelling or pain).

Driving and skilled tasks Patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of dizziness, hypotension and blurred vision.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Carfilzomib for previously treated multiple myeloma (November 2020) NICE TA657 Recommended with restrictions

▶ Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (April 2021) NICE TA695 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions
▶ Carfilzomib (Kyprolis ®) in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy [see also SMC2290] (January 2017) SMC No. 1171/16 Not recommended
▶ Carfilzomib (Kyprolis ®) in combination with dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (August 2017) SMC No. 1242/17 Recommended
▶ Carfilzomib (Kyprolis ®) in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy [for patients who have received only one prior therapy] (October 2020) SMC No. SMC2290 Recommended
| MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Powder for solution for infusion
EXCIPIENTS: May contain Sulfobutylether beta cyclodextrin sodium
ELECTROLYTES: May contain Sodium
▶ Kyprolis (Amgen Ltd)
Carfilzomib 10 mg Kyprolis 10mg powder for solution for infusion vials | 1 vialP £176.00 (Hospital only)
Carfilzomib 30 mg Kyprolis 30mg powder for solution for infusion vials | 1 vialP £528.00 (Hospital only)
Carfilzomib 60 mg Kyprolis 60mg powder for solution for infusion vials | 1 vialP £1,056.00 (Hospital only)

Ixazomib 01-May-2019

| DRUG ACTION Ixazomib is a proteasome inhibitor.
| INDICATIONS AND DOSE
Multiple myeloma in patients who have received at least one prior therapy, in combination with lenalidomide and dexamethasone (specialist use only)
▶ BY MOUTH
▶ Adult: 4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle, for dose adjustments due to side-effects, consult product literature
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
| CAUTIONS Risk of herpes zoster reactivation
CAUTIONS, FURTHER INFORMATION
▶ Herpes zoster reactivation Manufacturer advises consider concomitant antiviral prophylaxis to decrease the risk of herpes zoster reactivation.
| INTERACTIONS → Appendix 1: ixazomib
| SIDE-EFFECTS
▶ Common or very common Back pain . constipation . diarrhoea . increased risk of infection . nausea . neutropenia . peripheral neuropathy (monitor for symptoms) . peripheral oedema . skin reactions . thrombocytopenia . vomiting
▶ Rare or very rare Posterior reversible encephalopathy syndrome (PRES) (discontinue) . Stevens-Johnson syndrome . thrombotic microangiopathy . transverse myelitis . tumour lysis syndrome
▶ Frequency not known Appetite decreased . conjunctivitis . dizziness . dry eye . fatigue . hepatic disorders . hypokalaemia
| CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception in women of child-bearing potential and in men with a partner of child-bearing potential, during treatment and for at least 90 days after stopping treatment; additional barrier method recommended in women using hormonal contraceptives.
| PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.
| BREAST FEEDING Manufacturer advises avoid—no information available.
| HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).
Dose adjustments Manufacturer advises dose reduction to 3 mg in moderate to severe impairment.
| RENAL IMPAIRMENT
Dose adjustments Manufacturer advises reduce dose to 3 mg in severe impairment (creatinine clearance less than 30 mL/min). See p. 21.
| MONITORING REQUIREMENTS Manufacturer advises to monitor hepatic function regularly and adjust dose accordingly—consult product literature.
| PATIENT AND CARER ADVICE

Missed doses Manufacturer advises if less than 72 hours remain before the next scheduled dose, the missed dose should not be taken and the next dose should be taken at the normal time.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (February 2018) NICE TA505 Recommended with restrictions

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 23, 25

▶ Ninlaro (Takeda UK Ltd) A

Ixazomib (as Ixazomib citrate) 2.3 mg Ninlaro 2.3mg capsules | 3 capsuleP £6,336.00

Ixazomib (as Ixazomib citrate) 3 mg Ninlaro 3mg capsules | 3 capsuleP £6,336.00

Ixazomib (as Ixazomib citrate) 4 mg Ninlaro 4mg capsules | 3 capsuleP £6,336.00

ANTINEOPLASTIC DRUGS › PROTEIN KINASE INHIBITORS

Abemaciclib 06-Oct-2021

I DRUG ACTION Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6, which leads to disruption of cancer cell proliferation.

I INDICATIONS AND DOSE

Locally advanced or metastatic breast cancer (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 150 mg twice daily, for dose adjustments due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce abemaciclib dose to 100mg twice daily; in those already taking a reduced dose, consult product literature. If the CYP3A4 inhibitor is stopped, increase the abemaciclib dose (after 3–5 half lives of the inhibitor) to the dose used before starting the CYP3A4 inhibitor.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE: CDK4/6 INHIBITORS (ABEMACICLIB, PALBOCICLIB, RIBOCICLIB): REPORTS OF INTERSTITIAL LUNG DISEASE AND PNEUMONITIS, INCLUDING SEVERE CASES (JUNE 2021)

Interstitial lung disease and pneumonitis, in some cases severe or fatal, have been reported in patients being treated with CDK4/6 inhibitors, such as abemaciclib. Healthcare professionals are advised to ask patients taking abemaciclib about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnoea. Patients should be advised to seek advice right away if these symptoms occur. Healthcare professionals should ensure patients have a copy of the Patient Information Leaflet (PIL) for abemaciclib.

I INTERACTIONS → Appendix 1: abemaciclib

I SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . decreased leucocytes . diarrhoea . dizziness . embolism and thrombosis . excessive tearing . fatigue . fever . infection . muscle weakness . nausea . neutropenia . respiratory disorders . skin reactions . taste altered . thrombocytopenia . vomiting

I CONCEPTION AND CONTRACEPTION Manufacturer advises highly effective contraception in women of childbearing potential during treatment and for at least 3 weeks after completing treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment. Temporary or permanent withdrawal may be needed following increases in aminotransferases—

consult product literature.
Dose adjustments Manufacturer advises dose reduction to 150mg once daily in severe impairment.
I RENAL IMPAIRMENT Manufacturer advises caution in severe impairment—monitor for signs of toxicity.
I MONITORING REQUIREMENTS Manufacturer advises monitor full blood count, and alanine and aspartate aminotransferases before starting treatment, every 2 weeks for the first 2 months, monthly for the following 2 months, and as clinically indicated thereafter.
I PATIENT AND CARER ADVICE Patients should be instructed to start an antidiarrhoeal such as loperamide, increase oral fluids, and seek medical advice at the first sign of loose stools. Patients should also be instructed to seek medical advice if fever occurs.
Driving and skilled tasks Patients should be cautioned on the effects on driving and performance of skilled tasks—increased risk of fatigue and dizziness.
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (February 2019) NICE TA563 Recommended with restrictions
▶ Abemaciclib with fulvestrant for treating hormone receptorpositive, HER2-negative advanced breast cancer after endocrine therapy (September 2021) NICE TA725 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Abemaciclib (Verzenios ●) for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or in women who have received prior endocrine therapy (May 2019) SMC No. SMC2135 Recommended
▶ Abemaciclib (Verzenios ●) for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with fulvestrant as initial endocrine-based therapy or in women who have received prior endocrine therapy (May 2019) SMC No. SMC2179 Recommended with restrictions
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 3, 25
▶ Verzenios (Eli Lilly and Company Ltd) A
Abemaciclib 50 mg Verzenios 50mg tablets | 28 tabletP £1,475.00 (Hospital only) | 56 tabletP £2,950.00 (Hospital only)
Abemaciclib 100 mg Verzenios 100mg tablets | 28 tabletP £1,475.00 (Hospital only) | 56 tabletP £2,950.00 (Hospital only)
Abemaciclib 150 mg Verzenios 150mg tablets | 28 tabletP £1,475.00 (Hospital only) | 56 tabletP £2,950.00 (Hospital only)

Acalabrutinib 25-Jun-2021

I DRUG ACTION Acalabrutinib is a tyrosine kinase inihibitor.
I INDICATIONS AND DOSE
Chronic lymphocytic leukaemia (specialist use only)
▶ BY MOUTH
▶ Adult: 100 mg twice daily, doses should be taken approximately 12 hours apart, for dose adjustment,

interruption, or treatment discontinuation due to sideeffects—consult product literature
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CAUTIONS Exposure to sun (risk of skin cancer)—protect skin from exposure to sun . patients at high risk for thromboembolic disease—consider alternative treatment options to acalabrutinib . patients at increased risk for opportunistic infections—consider prophylaxis and monitor for signs and symptoms of infection . risk of haemorrhage—consider withholding acalabrutinib treatment for at least 3 days before and after surgery
I INTERACTIONS → Appendix 1: acalabrutinib
I SIDE-EFFECTS
▶ Common or very common Abdominal pain . anaemia . arrhythmias . arthralgia . asthenia . constipation . diarrhoea . dizziness . haemorrhage . headache . increased

risk of infection . intracranial haemorrhage . musculoskeletal pain . nausea . neutropenia . second primary malignancy . skin reactions . thrombocytopenia . vomiting

▶ Uncommon Hepatitis B reactivation . lymphocytosis . tumour lysis syndrome

▶ Frequency not known Cough . leucopenia . progressive multifocal leukoencephalopathy (PML) . sepsis

I PREGNANCY gAvoid unless potential benefit outweighs risk—toxicity in animal studies. MSee also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING gAvoid breast feeding during treatment and for 2 days after the last dose—present in milk in animal studies. M

I HEPATIC IMPAIRMENT gCaution in moderate impairment; avoid in severe impairment (risk of increased exposure). M

I RENAL IMPAIRMENT gCaution in severe impairment (no information available). M

I PRE-TREATMENT SCREENING Patients should be evaluated for hepatitis B virus status before starting treatment—consult product literature.

I PATIENT AND CARER ADVICE

Missed doses gIf a dose is more than 3 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. M

Driving and skilled tasks gPatients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and fatigue. M

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Acalabrutinib for treating chronic lymphocytic leukaemia [in adults with untreated chronic lymphocytic leukaemia] (April 2021) NICE TA689 Recommended with restrictions

▶ Acalabrutinib for treating chronic lymphocytic leukaemia [in adults with previously treated chronic lymphocytic leukaemia] (April 2021) NICE TA689 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Acalabrutinib (Calquence *) as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) [and in whom chemo-immunotherapy is unsuitable] (April 2021) SMC No. SMC2346 Recommended with restrictions

▶ Acalabrutinib (Calquence *) as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy (April 2021) SMC No. SMC2348 Recommended with restrictions

▶ Acalabrutinib (Calquence *) as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) [and who are ineligible for fludarabine, cyclophosphamide and rituximab therapy] (June 2021) SMC No. SMC2347 Recommended with restrictions

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

▶ Calquence (AstraZeneca UK Ltd) A

Acalabrutinib 100 mg Calquence 100mg capsules | 60 capsuleP £5,059.00 (Hospital only)

Afatinib 30-Sep-2021

I DRUG ACTION Afatinib is a protein kinase inhibitor.

I INDICATIONS AND DOSE

Treatment of locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, in patients who have not previously been treated with EGFR tyrosine kinase inhibitor

▶ BY MOUTH

▶ Adult: 40 mg once daily; increased if tolerated to up to 50 mg once daily, dose increase may be considered after 3 weeks at initial dose; consult product literature for details on dosing and dose adjustment due to side effects

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CAUTIONS Cardiac risk factors . conditions which may affect left ventricular ejection fraction—consider cardiac

monitoring, including assessment of left ventricular ejection fraction, at baseline and during treatment . diarrhoea—proactive management recommended (consult product literature) . exposure to sun (protect skin from exposure to sun) . history of keratitis . new pulmonary symptoms (including dyspnoea, cough, fever)—interrupt treatment until interstitial lung disease is excluded . severe dry eyes . signs and symptoms of keratitis—promptly refer to ophthalmologist for assessment . signs and symptoms of skin reaction—treat promptly and interrupt afatinib treatment if severe or if Stevens-Johnson syndrome suspected (consult product literature) . ulcerative keratitis . use of contact lenses . worsening pulmonary symptoms (including dyspnoea, cough, fever)—interrupt treatment until interstitial lung disease is excluded

INTERACTIONS → Appendix 1: afatinib

SIDE-EFFECTS

▶ Common or very common Appetite decreased . cystitis . dehydration . diarrhoea . dry eye . dyspepsia . epistaxis . eye inflammation . fever . hypokalaemia . muscle spasms . nausea . oral disorders . paronychia . renal impairment . rhinorrhoea . skin reactions . taste altered . vomiting . weight decreased

▶ Uncommon Interstitial lung disease . pancreatitis

▶ Rare or very rare Severe cutaneous adverse reactions (SCARs)

CONCEPTION AND CONTRACEPTION Ensure effective contraception during and for at least one month after treatment in women of childbearing potential.

PREGNANCY Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment (no information available).

Dose adjustments Manufacturer advises consider dose interruption if hepatic function worsens in mild to moderate impairment—consult product literature.

RENAL IMPAIRMENT gAvoid if eGFR less than 15 mL/minute/1.73m2 (no information available). M

Dose adjustments gCaution if eGFR 15–29 mL/minute/1.73m2 (risk of increased exposure)—monitor and adjust dose if not tolerated. MSee p. 21.

DIRECTIONS FOR ADMINISTRATION Manufacturer advises tablets should be taken whole on an empty stomach. Food should not be consumed for at least 3 hours before and at least 1 hour after each dose.

Giotrif ∘ tablets may be dispersed in approximately 100mL of noncarbonated water by stirring occasionally for up to 15 minutes (must not be crushed). The dispersion should be swallowed immediately, and the glass rinsed with the same volume of water which should also be swallowed. The dispersion can also be administered via a gastric tube.

PATIENT AND CARER ADVICE Patient counselling advised (administration).

Driving and skilled tasks Ocular adverse reactions may affect performance of skilled tasks e.g. driving.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-smallcell lung cancer (April 2014) NICE TA310 Recommended with restrictions

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25

▶ Giotrif (Boehringer Ingelheim Ltd)

Afatinib (as Afatinib dimaleate) 20 mg Giotrif 20mg tablets | 28 tabletP £2,023.28

Afatinib (as Afatinib dimaleate) 30 mg Giotrif 30mg tablets | 28 tabletP £2,023.28

Afatinib (as Afatinib dimaleate) 40 mg Giotrif 40mg tablets | 28 tabletP £2,023.28

Afatinib (as Afatinib dimaleate) 50 mg Giotrif 50mg tablets | 28 tabletP £2,023.28

Alectinib 31-Aug-2020

I DRUG ACTION Alectinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only)

▶ BY MOUTH

▶ Adult: 600 mg twice daily, for dose adjustments due to side-effects—consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I INTERACTIONS → Appendix 1: alectinib

I SIDE-EFFECTS

▶ Common or very common Acute kidney injury . anaemia . arrhythmias . constipation . diarrhoea . eye disorders . eye inflammation . hyperbilirubinaemia . musculoskeletal pain . myalgia . nausea . oedema . oral disorders . photosensitivity reaction . skin reactions . taste altered . vision disorders . vomiting . weight increased

▶ Uncommon Drug-induced liver injury . respiratory disorders

I CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective contraception during and for at least 3 months after stopping treatment.

I PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid—no information available.

I HEPATIC IMPAIRMENT

Dose adjustments Manufacturer advises reduce dose to 450mg twice daily in severe impairment.

I MONITORING REQUIREMENTS

▶ Manufacturer advises monitor creatine phosphokinase every 2 weeks for the first month and as clinically indicated thereafter in patients reporting symptoms of myalgia.

▶ Manufacturer advises monitor heart rate and blood pressure as clinically indicated.

▶ Manufacturer advises monitor liver function at baseline then every 2 weeks during the first 3 months of treatment and periodically thereafter as clinically indicated; more frequent monitoring should be performed in patients who develop aminotransferase and bilirubin elevations.

▶ Manufacturer advises monitor for symptoms of interstitial lung disease and pneumonitis.

I PATIENT AND CARER ADVICE

Photosensitivity Manufacturer advises patients should use a broad spectrum sunscreen and lip balm and be advised to avoid prolonged sun exposure during treatment, and for 7 days after discontinuation.

Myalgia Manufacturer advises patients should advised to report any unexplained muscle pain, tenderness or weakness.

Vomiting Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time.

Missed doses Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of symptomatic bradycardia and vision disorders.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Alectinib (Alecensa ®) for untreated ALK-positive advanced non-small cell lung cancer (August 2018) NICE TA536 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Alectinib hydrochloride (Alecensa ®) as monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) (August 2018) SMC No. SMC2012 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 11, 21
ELECTROLYTES: May contain Sodium
▶ Alecensa (Roche Products Ltd) A
Alectinib (as Alectinib hydrochloride) 150 mg Alecensa 150mg capsules | 224 capsuleP £5,032.00

Alpelisib 20-Oct-2020

I DRUG ACTION Alpelisib is an alpha-specific class 1 protein kinase inhibitor.
I INDICATIONS AND DOSE
Locally advanced or metastatic breast cancer (in combination with fulvestrant) [in postmenopausal women and men] (initiated by a specialist)
▶ BY MOUTH
▶ Adult: 300 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CONTRA-INDICATIONS History of severe cutaneous reactions . osteonecrosis of the jaw
I CAUTIONS History of diabetes mellitus (risk of hyperglycaemia)
I INTERACTIONS → Appendix 1: alpelisib
I SIDE-EFFECTS
▶ Common or very common Acute kidney injury . alopecia . anaemia . appetite decreased . asthenia . dehydration . diarrhoea . dry eye . dry mouth . electrolyte imbalance . eyelid oedema . facial swelling . fever . gastrointestinal discomfort . headache . hypersensitivity . hypertension . increased risk of infection . insomnia . lymphoedema . mucosal abnormalities . muscle complaints . nausea . oedema . oral disorders . osteonecrosis of jaw . respiratory disorders . skin reactions . taste altered . urosepsis . vision blurred . vomiting . vulvovaginal dryness . weight decreased
▶ Uncommon Diabetic ketoacidosis . ketoacidosis . pancreatitis . severe cutaneous adverse reactions (SCARs)
▶ Frequency not known Hyperglycaemia
I CONCEPTION AND CONTRACEPTION Manufacturer advises male patients should use effective contraception during treatment and for one week after last dose if their partner is pregnant or of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. The effect on human fertility is not known—impairment of fertility has been observed in animal studies.
I RENAL IMPAIRMENT Manufacturer advises use with caution in severe renal impairment—no information available.
I MONITORING REQUIREMENTS Manufacturer advises assess fasting plasma glucose and HbA1c levels before initiation and monitor frequently in the first 4 weeks of treatment—consult product literature.
I PATIENT AND CARER ADVICE
Vomiting Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time.
Missed doses Manufacturer advises if dose is more than 9 hours late, the missed dose should not be taken and the next dose should be taken at the usual time.
Driving and skilled tasks Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of fatigue or blurred vision.
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 25, 21
▶ Piqray (Novartis Pharmaceuticals UK Ltd) A
Alpelisib 50 mg Piqray 50mg tablets | 28 tabletPs(Hospital only)
Alpelisib 150 mg Piqray 150mg tablets | 56 tabletP £4,082.14 (Hospital only)
Alpelisib 200 mg Piqray 200mg tablets | 28 tabletP £4,082.14 (Hospital only)

Avapritinib 17-Nov-2020

I DRUG ACTION Avapritinib is a tyrosine kinase inhibitor.
I INDICATIONS AND DOSE
Gastro-intestinal stromal tumours (initiated by a specialist)
▶ BY MOUTH

▶ Adult: 300 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ gIf concurrent use of moderate CYP3A4 inhibitors is unavoidable, decrease the initial avapritinib dose to 100mg once daily. M

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CAUTIONS Risk factors for haemorrhage . susceptibility to QT-interval prolongation

I INTERACTIONS → Appendix 1: avapritinib

I SIDE-EFFECTS

▶ Common or very common Abdominal pain . acute kidney injury . alopecia . anaemia . anxiety . appetite decreased . arthralgia . ascites . asthenia . back pain . CNS haemorrhage . cognitive impairment . concentration impaired . confusion . constipation . cough . dementia . depression . diarrhoea . dizziness . drowsiness . dry mouth . dysphagia . dyspnoea . electrolyte imbalance . excessive tearing . eye inflammation . facial swelling . feeling cold . fever . fluid imbalance . gastrointestinal disorders . haemorrhage . hair colour changes . headache . hyperbilirubinaemia . hypertension . hypoalbuminaemia . insomnia . malaise . memory impairment . movement disorders . muscle complaints . nasal congestion . nausea . oedema . oral disorders . peripheral neuropathy . peripheral swelling . photosensitivity reaction . psychiatric disorder .QT interval prolongation . respiratory disorders . skin reactions . speech impairment . taste altered . thrombocytopenia . tremor . vertigo . vision disorders . vomiting . weight changes

▶ Uncommon Encephalopathy . pericardial effusion . tumour haemorrhage

I CONCEPTION AND CONTRACEPTION gFemales of childbearing potential should use effective contraception during treatment and for one month after last treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. M

I PREGNANCY gAvoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. M

I BREAST FEEDING gAvoid during treatment and for at least 2 weeks after the last dose—no information available. M

I HEPATIC IMPAIRMENT gAvoid in severe impairment (no information available). M

I RENAL IMPAIRMENT gAvoid in severe impairment or end-stage renal disease (no information available). M

I PATIENT AND CARER ADVICE

Vomiting gIf vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time. M

Photosensitivity gAvoid or minimise exposure to direct sunlight; patients should be advised to use a high protection sunscreen and wear protective clothing. M

Missed doses gIf a dose is more than 16 hours late, the missed dose should not be taken and the next dose should be taken at the usual time. M

Driving and skilled tasks gPatients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of cognitive effects. M

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 23, 25

▶ Ayvakyt (Blueprint Medicines (UK) Ltd) A

Avapritinib 100 mg Ayvakyt 100mg tablets | 30 tabletP
£26,667.00 (Hospital only)

Avapritinib 200 mg Ayvakyt 200mg tablets | 30 tabletP
£26,667.00 (Hospital only)

Avapritinib 300 mg Ayvakyt 300mg tablets | 30 tabletP
£26,667.00 (Hospital only)

Axitinib 15-Oct-2020

DRUG ACTION Axitinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Advanced renal cell carcinoma (specialist use only)

▶ BY MOUTH

▶ Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with axitinib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CONTRA-INDICATIONS Recent active gastro-intestinal bleeding . untreated brain metastases

CAUTIONS Hypertension . risk factors for aneurysm or artery dissection

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

INTERACTIONS → Appendix 1: axitinib

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . arthralgia . asthenia . constipation . cough . dehydration . diarrhoea . dizziness . dysphonia . dyspnoea . electrolyte imbalance . embolism and thrombosis . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . heart failure . hyperbilirubinaemia . hypertension . hyperthyroidism . hypothyroidism . mucositis . myalgia . nausea . oral disorders . oropharyngeal pain . pain in extremity . polycythaemia . proteinuria . renal failure . skin reactions . taste altered . thrombocytopenia . tinnitus . vomiting . weight decreased

▶ Uncommon Leucopenia . neutropenia . posterior reversible encephalopathy syndrome (PRES)

▶ Frequency not known Aneurysm . artery dissection

CONCEPTION AND CONTRACEPTION Effective contraception required during and for up to 1 week after treatment.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment—no information available.

Dose adjustments Manufacturer advises reduce dose in moderate impairment.

MONITORING REQUIREMENTS

▶ Monitor for thyroid dysfunction.

▶ Monitor haemoglobin or haematocrit before and during treatment.

▶ Monitor for symptoms of gastro-intestinal perforation.

▶ Monitor for symptoms of fistula.

▶ Monitor for proteinuria before and during treatment.

▶ Monitor liver function before and during treatment.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (February 2015) NICE TA333 Recommended with restrictions

▶ Avelumab with axitinib for untreated advanced renal cell carcinoma (September 2020) NICE TA645 Recommended

▶ Pembrolizumab with axitinib for untreated advanced renal cell carcinoma (September 2020) NICE TA650 Not recommended

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Inlyta (Pfizer Ltd)
Axitinib 1 mg Inlyta 1mg tablets | 56 tabletP £703.40 (Hospital only)
Axitinib 3 mg Inlyta 3mg tablets | 56 tabletP £2,110.20 (Hospital only)
Axitinib 5 mg Inlyta 5mg tablets | 56 tabletP £3,517.00 (Hospital only)
Axitinib 7 mg Inlyta 7mg tablets | 56 tabletP £4,923.80 (Hospital only)

Binimetinib 05-Mar-2019

I DRUG ACTION Binimetinib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically mitogenactivated extracellular kinases MEK 1 and 2, thereby inhibiting BRAF V600 mutation-positive cell growth.
I INDICATIONS AND DOSE
Unresectable or metastatic melanoma with a BRAF V600 mutation (in combination with encorafenib) (specialist use only)
▶ BY MOUTH
▶ Adult: 45 mg twice daily, for dose adjustments due to side-effects, consult product literature
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CONTRA-INDICATIONS History of retinal vein occlusion
I CAUTIONS Left ventricular dysfunction (ejection fraction below 50%, or below the institutional lower limits of normal) . neuromuscular conditions associated with elevated creatine kinase and rhabdomyolysis . risk factors for retinal vein occlusion . risk factors for venous thromboembolism
I SIDE-EFFECTS
▶ Common or very common Alopecia . anaemia . angioedema . arthralgia . constipation . detachment of retinal pigment epithelium . diarrhoea . dizziness . embolism and thrombosis . eye inflammation . fatigue . fever . fluid retention . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . heart failure . hypersensitivity . hypersensitivity vasculitis . hypertension . intracranial haemorrhage . left ventricular dysfunction . lip squamous cell carcinoma . muscle complaints . muscle weakness . myopathy . nausea . neoplasms . nerve disorders . oedema . pain . panniculitis . photosensitivity reaction . renal failure . skin reactions . taste altered . ulcerative colitis . vision disorders . vomiting
▶ Uncommon Facial paralysis . pancreatitis
▶ Frequency not known Respiratory disorders . retinal occlusion (discontinue permanently)
I CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective contraception during and for at least one month after stopping treatment.
I PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.
I BREAST FEEDING Manufacturer advises avoid—no information available.
I HEPATIC IMPAIRMENT Manufacturer advises avoid in moderate or severe impairment (increased exposure).
I MONITORING REQUIREMENTS
▶ Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.
▶ Manufacturer advises assess left ventricular ejection fraction before treatment, one month after starting treatment, then every 3 months or more frequently as clinically indicated.
▶ Manufacturer advises monitor for visual disturbances.
▶ Manufacturer advises monitor blood pressure before and during treatment.
▶ Manufacturer advises monitor creatine kinase and creatinine levels monthly during the first 6 months of treatment, and as clinically indicated.

I PATIENT AND CARER ADVICE
Missed doses Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (February 2019) NICE TA562 Recommended with restrictions
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 3, 25
▶ Mektovi (Pierre Fabre Ltd) A
Binimetinib 15 mg Mektovi 15mg tablets | 84 tabletP £2,240.00 (Hospital only)

Bosutinib 05-Dec-2019

I INDICATIONS AND DOSE
Previously treated chronic, accelerated and blast phase Philadelphia chromosome-positive chronic myeloid leukaemia (specialist use only)
▶ BY MOUTH
▶ Adult: 500 mg once daily, consult product literature for dose adjustment due to side-effects, or incomplete haematologic response by week 8, or incomplete cytogenetic response by week 12
Newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myeloid leukaemia (specialist use only)
▶ BY MOUTH
▶ Adult: 400 mg once daily, consult product literature for dose adjustment due to side-effects, or failure to demonstrate breakpoint cluster region-Abelson (BCRABL) transcripts _10% by month 3
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS
An EU wide review has concluded that bosutinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.
I CAUTIONS Cardiac disease . hepatitis B infection . history of pancreatitis—withhold treatment if lipase elevated and abdominal symptoms occur . history of QT prolongation—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment . recent cardiac event—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment . risk factors for QT prolongation—monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment . significant gastrointestinal disorder
CAUTIONS, FURTHER INFORMATION
▶ Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for

patients who test positive for hepatitis B virus and in those with active infection.
I INTERACTIONS → Appendix 1: bosutinib
I SIDE-EFFECTS
▶ Common or very common Anaemia . appetite decreased . arthralgia . asthenia . chest discomfort . cough . dehydration . diarrhoea . dizziness . dyspnoea . electrolyte imbalance . fever . gastritis . gastrointestinal discomfort . haemorrhage . headache . hepatic disorders . hyperbilirubinaemia . hyperlipasaemia . hypertension . increased risk of infection . leucopenia . long QT syndrome . malaise . myalgia . nausea . neutropenia . oedema . pain . pericardial effusion .QT interval prolongation . renal

impairment . respiratory disorders . skin reactions . taste altered . thrombocytopenia . tinnitus . vomiting

▶ Uncommon Pancreatitis . pericarditis . pulmonary hypertension . pulmonary oedema . tumour lysis syndrome

▶ Frequency not known Hepatitis B reactivation . severe cutaneous adverse reactions (SCARs)

ı CONCEPTION AND CONTRACEPTION Effective contraception required during treatment in women.

ı PREGNANCY Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—no information available.

ı HEPATIC IMPAIRMENT Manufacturer advises avoid.

ı RENAL IMPAIRMENT

Dose adjustments For chronic, accelerated and blast phase Philadelphia chromosome-positive chronic myeloid leukaemia, manufacturer advises reduce dose to 400mg in moderate impairment; reduce dose to 300mg in severe impairment; consult product literature for dose adjustment due to side-effects, or incomplete haematological, cytogenetic, or molecular response.

For newly-diagnosed chronic phase Philadelphia chromosome-positive chronic myeloid leukaemia, manufacturer advises reduce dose to 300mg in moderate impairment; reduce dose to 200mg in severe impairment; consult product literature for dose adjustment due to sideeffects, or incomplete haematological, cytogenetic, or molecular response.

ı MONITORING REQUIREMENTS

▶ Manufacturer advises monitor liver function before treatment initiation, then monthly for the first 3 months and thereafter as clinically indicated—consult product literature for management of raised transaminases.

▶ Manufacturer advises monitor full blood count weekly for the first month and then monthly thereafter or as clinically indicated.

▶ Manufacturer advises monitor for signs and symptoms of fluid retention (including pericardial effusion, pleural effusion and pulmonary oedema).

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Bosutinib for previously treated chronic myeloid leukaemia (August 2016) NICE TA401 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

▶ Bosulif (Pfizer Ltd) A

Bosutinib 100 mg Bosulif 100mg tablets | 28 tabletP £859.17 (Hospital only)

Bosutinib 400 mg Bosulif 400mg tablets | 28 tabletP £3,436.67 (Hospital only)

Bosutinib 500 mg Bosulif 500mg tablets | 28 tabletP £3,436.67 (Hospital only)

Brigatinib 12-Feb-2021

ı DRUG ACTION Brigatinib is a tyrosine kinase inhibitor.

ı INDICATIONS AND DOSE

Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only)

▶ BY MOUTH

▶ Adult: Initially 90 mg once daily for 7 days, then increased to 180 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce brigatinib dose to 90mg once daily; in those starting treatment or already taking a reduced dose, consult product literature.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı INTERACTIONS → Appendix 1: brigatinib

ı SIDE-EFFECTS

▶ Common or very common Anaemia . appetite decreased . arrhythmias . arthralgia . asthenia . cataract . chest discomfort . constipation . cough . diarrhoea . dizziness . dry mouth . dyspnoea . electrolyte imbalance . eye disorders . eye inflammation . facial swelling . fever .

flatulence . gastrointestinal discomfort . glaucoma . headaches . hyperbilirubinaemia . hyperglycaemia . hyperinsulinaemia . hypertension . increased risk of infection . insomnia . memory loss . muscle complaints . musculoskeletal discomfort . nausea . nerve disorders . neurotoxicity . oedema . oral disorders . pain . palpitations . peripheral swelling . photosensitivity reaction .QT interval prolongation . respiratory disorders . sensation abnormal . skin reactions . taste altered . vision disorders . vomiting . weight decreased

▶ Uncommon Pancreatitis

I CONCEPTION AND CONTRACEPTION Manufacturer advises effective non-hormonal contraception in females of childbearing potential during and for at least 4 months after treatment. Male patients with partners of childbearing potential should use effective contraception during and for at least 3 months after treatment.

I PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment.

Dose adjustments Manufacturer advises dose reduction to 60 mg once daily for 7 days, then increase to 120mg once daily in severe impairment.

I RENAL IMPAIRMENT Manufacturer advises caution in severe impairment.

Dose adjustments Manufacturer advises dose reduction to 60 mg once daily for 7 days, then increase to 90 mg once daily in severe impairment.

I MONITORING REQUIREMENTS

▶ Manufacturer advises monitor for new or worsening respiratory symptoms, particularly in the first week of treatment—promptly investigate if pneumonitis suspected (consult product literature).

▶ Manufacturer advises monitor blood pressure, heart rate, creatine phosphokinase, amylase, and lipase regularly.

▶ Manufacturer advises monitor liver function at baseline, then every 2 weeks during the first 3 months of treatment, and periodically thereafter.

▶ Manufacturer advises monitor fasting serum glucose at baseline and periodically thereafter.

I PATIENT AND CARER ADVICE Manufacturer advises patients and carers should be told to report symptoms of visual disturbance, or unexplained muscle pain, tenderness, or weakness.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbance, dizziness, or fatigue.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (March 2019) NICE TA571 Recommended with restrictions

▶ Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor (January 2021) NICE TA670 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Brigatinib (Alunbrig ⁎) as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase positive (ALK +) advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib (June 2019) SMC No. SMC2147 Recommended

▶ Brigatinib (Alunbrig ⁎) as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor (January 2021) SMC No. SMC2314 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Form unstated

CAUTIONARY AND ADVISORY LABELS 25

▶ Alunbrig (Takeda UK Ltd) A

Alunbrig 90mg/180mg tablets treatment initiation pack |

28 tabletP £4,900.00
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Alunbrig (Takeda UK Ltd) A
Brigatinib 30 mg Alunbrig 30mg tablets | 28 tabletP £1,225.00
Brigatinib 90 mg Alunbrig 90mg tablets | 28 tabletP £3,675.00
Brigatinib 180 mg Alunbrig 180mg tablets | 28 tabletP £4,900.00

Cabozantinib 22-Nov-2021

I DRUG ACTION Cabozantinib is an inhibitor of several protein kinases.
I INDICATIONS AND DOSE
Progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (initiated by a specialist)
▶ BY MOUTH USING CAPSULES
▶ Adult: 140 mg once daily, for dose adjustment or treatment interruption due to side-effects, consult product literature (closely monitor for first 8 weeks of therapy)
Advanced renal cell carcinoma (as monotherapy) (initiated by a specialist) | Hepatocellular carcinoma (initiated by a specialist)
▶ BY MOUTH USING TABLETS
▶ Adult: 60 mg once daily, for dose adjustment or treatment interruption due to side-effects, consult product literature (closely monitor for first 8 weeks of therapy)
Advanced renal cell carcinoma (in combination with nivolumab) (initiated by a specialist)
▶ BY MOUTH USING TABLETS
▶ Adult: 40 mg once daily, for dose adjustment or treatment interruption due to side-effects, consult product literature (closely monitor for first 8 weeks of therapy)
DOSE EQUIVALENCE AND CONVERSION
▶ Cabozantinib tablets and capsules are not bioequivalent—consult product literature when switching formulations.
IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)
A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with cabozantinib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CONTRA-INDICATIONS Reversible posterior leucoencephalopathy syndrome
I CAUTIONS Hypertension . palmar-plantar erythrodysaesthesia syndrome—consider treatment interruption if severe and restart at a lower dose when resolved to grade 1 . patients at increased risk of fistulas—consult product literature . patients at increased risk of gastro-intestinal perforation—consult product literature . patients at increased risk of intra-abdominal abscess—consult product literature . patients at risk of haemorrhage (including tumour involvement of the trachea or bronchi)—discontinue if symptoms develop . patients at risk of thromboembolic events including myocardial infarction—discontinue if symptoms develop . risk factors for aneurysm or artery dissection . risk of osteonecrosis of the jaw . susceptibility to QT-interval prolongation (e.g. cardiac disease, electrolyte disturbances, bradycardia, concomitant use of drugs that prolong the QT interval)
CAUTIONS, FURTHER INFORMATION
▶ Elective surgery Withhold treatment for at least 28 days before elective surgery and restart only if adequate wound healing—discontinue in patients with wound healing complications requiring medical intervention.
▶ Risk of osteonecrosis of the jaw Discontinue treatment at least 28 days before elective invasive dental procedures—monitor for symptoms before and during treatment and discontinue if osteonecrosis develops.
▶ Monitoring of blood pressure The MHRA advises to monitor

blood pressure regularly—consult product literature if hypertension occurs during treatment.

INTERACTIONS → Appendix 1: cabozantinib

SIDE-EFFECTS

▶ Common or very common Abscess . alopecia . anaemia . anxiety . appetite decreased . arrhythmias . arthralgia . asthenia . chills . cholelithiasis . confusion . constipation . cough . dehydration . depression . diarrhoea . dizziness . dry mouth . dyslipidaemia . dysphagia . dysphonia . dyspnoea . dysuria . ear pain . electrolyte imbalance . embolism and thrombosis . encephalopathy . fistula .

gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . hair changes . headache . healing impaired . hyperbilirubinaemia . hyperglycaemia . hypertension . hypoalbuminaemia . hypoglycaemia . hypotension . hypothyroidism . increased risk of infection . lymphopenia . mucositis . muscle spasms . nausea . nerve disorders . neutropenia . oedema . oral disorders . oropharyngeal pain . osteonecrosis of jaw . pain . pallor . pancreatitis . paraesthesia . peripheral coldness . proteinuria . respiratory disorders . skin reactions . stroke . taste altered . thrombocytopenia . tinnitus . tracheo-oesophageal fistula . tremor . vision blurred . vomiting . weight decreased

▶ Uncommon Abnormal dreams . acute kidney injury . amenorrhoea . angina pectoris . ataxia . cataract . concentration impaired . conjunctivitis . cyst . delirium . hearing impairment . hepatic disorders . loss of consciousness . rhabdomyolysis . seizure . skin ulcer . speech disorder . telangiectasia . throat oedema . wound complications

▶ Frequency not known Aneurysm . artery dissection . myocardial infarction

CONCEPTION AND CONTRACEPTION Patients and their sexual partners must use effective contraception (in addition to barrier method) during treatment and for at least 4 months after the last dose.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises discontinue breast-feeding during treatment and for at least 4 months after the last dose.

HEPATIC IMPAIRMENT For capsules manufacturer advises caution in mild to moderate impairment (risk of increased exposure); avoid in severe impairment (no information available). For tablets manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

Dose adjustments For capsules manufacturer advises dose reduction to 60 mg once daily in mild to moderate impairment.

RENAL IMPAIRMENT gCaution in mild to moderate impairment; avoid in severe impairment (no information available). M

MONITORING REQUIREMENTS

▶ gMonitor urine protein regularly and discontinue if nephrotic syndrome develops.

▶ Monitor blood pressure, ECG and electrolytes during treatment.

▶ Measure baseline thyroid function before treatment and monitor during treatment.

▶ Perform liver function tests before starting, and monitor during treatment.

▶ Monitor platelet counts during treatment. M

PATIENT AND CARER ADVICE Food should not be consumed for at least 2 hours before and at least 1 hour after each dose.

Driving and skilled tasks Fatigue and weakness may affect performance of skilled tasks e.g. driving.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Cabozantinib for previously treated advanced renal cell carcinoma (August 2017) NICE TA463 Recommended
▶ Cabozantinib for untreated advanced renal cell carcinoma (October 2018) NICE TA542 Recommended with restrictions
▶ Cabozantinib for treating medullary thyroid cancer (March 2018) NICE TA516 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Cabozantinib (Cabometyx ®) for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy (June 2017) SMC No. 1234/17 Recommended
▶ Cabozantinib (Cabometyx ®) for treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk per IMDC criteria (February 2019) SMC No. SMC2136 Not recommended
▶ Cabozantinib (Cabometyx ®) in combination with nivolumab for the first-line treatment of advanced renal cell carcinoma in adults (October 2021) SMC No. SMC2386 Recommended
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Form unstated
CAUTIONARY AND ADVISORY LABELS 23, 25
▶ Cometriq (Ipsen Ltd)
Cometriq 20mg capsules and Cometriq 80mg capsules | 56 capsuleP £4,800.00 | 112 capsuleP £4,800.00
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Cabometyx (Ipsen Ltd)
Cabozantinib (as Cabozantinib s-malate) 20 mg Cabometyx 20mg tablets | 30 tabletP £5,143.00 (Hospital only)
Cabozantinib (as Cabozantinib s-malate) 40 mg Cabometyx 40mg tablets | 30 tabletP £5,143.00 (Hospital only)
Cabozantinib (as Cabozantinib s-malate) 60 mg Cabometyx 60mg tablets | 30 tabletP £5,143.00 (Hospital only)
Capsule
CAUTIONARY AND ADVISORY LABELS 25
EXCIPIENTS: May contain Gelatin
▶ Cometriq (Ipsen Ltd)
Cabozantinib (as Cabozantinib s-malate) 20 mg Cometriq 20mg capsules | 84 capsuleP £4,800.00
Cabozantinib (as Cabozantinib s-malate) 80 mg Cometriq 80mg capsules | 7 capsulePs

Ceritinib 10-Jun-2021

I DRUG ACTION Ceritinib is a tyrosine kinase inhibitor, with particular activity against anaplastic lymphoma kinase (ALK).
I INDICATIONS AND DOSE
First-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only) | Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously treated with crizotinib (specialist use only)
▶ BY MOUTH
▶ Adult: 450 mg once daily, dose interruption, dose reduction or discontinuationmay be required based on individual safety and tolerability—consult product literature; discontinue treatment if patient unable to tolerate at least 150mg daily
DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce the dose by one-third (rounded to the nearest multiple of the 150mg dosage form).
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CONTRA-INDICATIONS Congenital long QT syndrome
I CAUTIONS Diabetes mellitus . history or susceptibility to QT-interval prolongation
CAUTIONS, FURTHER INFORMATION
▶ QT-interval prolongation QT-interval prolongation has been observed in clinical studies, which may lead to an increased risk for ventricular tachyarrhythmias (e.g.

torsade de pointes) or sudden death. Risk factors include pre-existing bradycardia, other relevant pre-existing cardiac disease or electrolyte disturbances; manufacturer advises to monitor ECG and electrolytes periodically.
I INTERACTIONS → Appendix 1: ceritinib
I SIDE-EFFECTS
▶ Common or very common Anaemia . appetite decreased . arrhythmias . asthenia . azotaemia . constipation .

diarrhoea . dysphagia . gastrointestinal discomfort . gastrooesophageal reflux disease . hepatic disorders . hyperbilirubinaemia . hyperglycaemia . hypophosphataemia . nausea . oesophageal disorder . pericardial effusion . pericarditis .QT interval prolongation . renal impairment . respiratory disorders . skin reactions . vision disorders . vitreous floater . vomiting . weight decreased

▶ Uncommon Pancreatitis

SIDE-EFFECTS, FURTHER INFORMATION Gastro-intestinal effects Manufacturer advises monitor for signs of gastrointestinal toxicity and consider dose reduction or discontinuation of treatment.

Interstitial lung disease Manufacturer advises monitor patients who exhibit pulmonary symptoms and consider dose reduction or discontinuation of treatment.

ı CONCEPTION AND CONTRACEPTION Manufacturer recommends effective contraception in women of childbearing potential during treatment and for up to 3 months after discontinuation of treatment.

ı PREGNANCY Manufacturer advises avoid unless essential—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—no information available.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (limited information available).

Dose adjustments Manufacturer advises reduce dose by approx. 33% in severe impairment (round to the nearest multiple of the 150mg dosage strength).

ı RENAL IMPAIRMENT gCaution in severe impairment (no information available). M

ı MONITORING REQUIREMENTS

▶ Manufacturer advises monitor fasting plasma-glucose concentration, amylase and lipase levels before treatment initiation and periodically thereafter as clinically indicated.

▶ Manufacturer advises measure baseline liver function, then monitor every 2 weeks for the first three months of treatment and monthly thereafter; if transaminases are elevated, more frequent monitoring should be performed as clinically indicated.

▶ Manufacturer advises monitor for pulmonary symptoms indicative of interstitial lung disease and pneumonitis—discontinue treatment if diagnosis confirmed; also monitor heart rate and blood pressure regularly.

ı DIRECTIONS FOR ADMINISTRATION Manufacturer advises Zykadia ∘ tablets should be taken with food at the same time each day—consult product literature for dosing information if patients are unable to take tablets with food.

ı PATIENT AND CARER ADVICE Patients and carers should be counselled on the administration of tablets.

Missed doses Manufacturer advises if a patient vomits during a course of treatment or if a dose is more than 12 hours late, the replacement or missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of fatigue and vision disorders.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Ceritinib for previously treated anaplastic lymphoma kinasepositive non-small cell lung cancer (June 2016) NICE TA395 Recommended with restrictions

▶ Ceritinib for untreated ALK-positive non-small cell lung cancer (January 2018) NICE TA500 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Ceritinib (Zykadia ∘) for treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced nonsmall cell lung cancer (NSCLC) previously treated with crizotinib (December 2015) SMC No. 1097/15 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

▶ Zykadia (Novartis Pharmaceuticals UK Ltd)

Ceritinib 150 mg Zykadia 150mg tablets | 84 tabletP £2,757.13 (Hospital only)

Cobimetinib 30-Apr-2019

ı DRUG ACTION Cobimetinib is a mitogen-activated protein

kinase (MAPK) inhibitor.

| INDICATIONS AND DOSE

Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma (in combination with vemurafenib) (specialist use only)

▶ BY MOUTH

▶ Adult: 60 mg once daily for 21 days; subsequent cycles repeated after a 7-day interval, for dose adjustment due to side-effects—consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

| CAUTIONS Left ventricular dysfunction . risk factors for bleeding

| INTERACTIONS → Appendix 1: cobimetinib

| SIDE-EFFECTS

▶ Common or very common Anaemia . basal cell carcinoma . chills . dehydration . diarrhoea . electrolyte imbalance . fever . haemorrhage . hyperglycaemia . hypertension . nausea . photosensitivity . pneumonitis . retinal detachment . retinopathy . skin reactions . sunburn . vision disorders . vomiting

▶ Uncommon Rhabdomyolysis

▶ Frequency not known Intracranial haemorrhage

| CONCEPTION AND CONTRACEPTION Manufacturer advises use of two effective contraceptive methods during treatment and for at least 3 months after stopping treatment.

| PREGNANCY Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

| BREAST FEEDING Manufacturer advises avoid—no information available.

| HEPATIC IMPAIRMENT Manufacturer advises caution.

| RENAL IMPAIRMENT Manufacturer advises caution in severe impairment—limited information available.

| MONITORING REQUIREMENTS

▶ Creatine kinase elevation Manufacturer advises baseline creatine kinase and creatinine levels should be measured before starting treatment, and then at monthly intervals during treatment or as clinically indicated—consult product literature if elevated.

▶ Left ventricular function Manufacturer advises ejection fraction should be evaluated before initiation of treatment, then after the first month of treatment and at least every 3 months thereafter (or as clinically indicated) until treatment discontinuation.

▶ Liver function Manufacturer advises liver function should be evaluated before initiation of treatment and monthly thereafter (or more frequently as clinically indicated).

▶ Visual disturbances Manufacturer advises assess for new or worsening visual disturbances at each visit; if symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended.

| PATIENT AND CARER ADVICE

Vomiting Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time.

Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.

| NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (October 2016) NICE TA414 Not recommended

| MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Cotellic (Roche Products Ltd)

Cobimetinib (as Cobimetinib hemifumarate) 20 mg Cotellic 20mg tablets | 63 tabletP £4,275.67

Crizotinib 30-Jan-2022

| DRUG ACTION Crizotinib is a tyrosine kinase inhibitor.

ı INDICATIONS AND DOSE

Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only) | ROS1-positive advanced non-small cell lung cancer (specialist use only)

▶ BY MOUTH

▶ Adult: 250 mg twice daily, consult product literature for information on dose adjustments based on individual patient safety and tolerability

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE (NOVEMBER 2015): RISK OF CARDIAC FAILURE

Severe, sometimes fatal cases of cardiac failure have been reported in patients treated with crizotinib. The MHRA has issued the following advice:

. monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention)

. consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur

ı CAUTIONS History of diverticulitis (risk of gastrointestinal perforation—discontinue treatment if gastrointestinal perforation occurs) . metastases of gastrointestinal tract (risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs) . patients with susceptibility to QTprolongation (including bradycardia, history of cardiac disease, concomitant use of drugs that prolong QT interval, and electrolyte disturbances)—periodic renal monitoring required . risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs . vision disorders reported—consider full ophthalmological evaluation if vision disorder worsens or persists

CAUTIONS, FURTHER INFORMATION

▶ Fatal interstitial lung disease and pneumonitis Fatal interstitial lung disease and pneumonitis reported (monitor patients with pulmonary symptoms, withdraw treatment if suspected, and permanently discontinue treatment if diagnosed).

ı INTERACTIONS → Appendix 1: crizotinib

ı SIDE-EFFECTS

▶ Common or very common Anaemia . appetite decreased . arrhythmias . constipation . diarrhoea . dizziness . fatigue . gait abnormal . gastrointestinal discomfort . gastrointestinal disorders . heart failure . hepatic function abnormal . hypogonadism . hypophosphataemia . leucopenia . local swelling . movement disorders . muscle atrophy . muscle tone decreased . muscle weakness . nausea . nerve disorders . neuralgia . neurotoxicity . neutropenia . oedema . periorbital oedema . peroneal nerve palsy . pulmonary oedema .QT interval prolongation . renal abscess . renal cyst . respiratory disorders . sensation abnormal . skin reactions . syncope . taste altered . vision disorders . vitreous floater . vomiting

▶ Uncommon Gastrointestinal perforation (including fatal cases) . hepatic failure (including fatal cases) . renal impairment

SIDE-EFFECTS, FURTHER INFORMATION Consider reducing the dose, or interrupting or stopping treatment if symptoms of cardiac failure occur.

ı CONCEPTION AND CONTRACEPTION Ensure effective contraception during and for at least 90 days after treatment.

ı PREGNANCY Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Avoid—no information available.

ı HEPATIC IMPAIRMENT Manufacturer advises use with caution.

Dose adjustments Manufacturer advises reduce dose in moderate to severe impairment—consult product literature.

ı RENAL IMPAIRMENT

Dose adjustments gReduce dose to 250mg once daily in severe impairment not requiring peritoneal dialysis or haemodialysis, may be increased to 200mg twice daily after at least 4 weeks, based on individual assessment of safety and tolerability. M

ı MONITORING REQUIREMENTS Monitor liver function once

a week during the first 2 months of treatment, then at least monthly thereafter and as clinically indicated. Monitor ECG and electrolytes (correct if abnormal) in all patients before starting treatment, then periodically and as clinically indicated thereafter. Monitor for signs and symptoms of treatment emergent bradycardia (including syncope, dizziness and hypotension)—monitor blood pressure and heart rate regularly.

ı PATIENT AND CARER ADVICE Counsel all patients on the early signs and symptoms of gastrointestinal perforation—advice to seek immediate medical attention.

Driving and skilled tasks Symptomatic bradycardia (including syncope, dizziness and hypotension), vision disorder and fatigue may affect performance of skilled tasks (e.g. driving or operating machinery).

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

1052 Targeted therapy responsive malignancy BNF 84

Immune system and malignant disease

NICE decisions

▶ Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (September 2016) NICE TA406 Recommended with restrictions

▶ Crizotinib for previously treated anaplastic lymphoma kinasepositive advanced non-small-cell lung cancer (December 2016) NICE TA422 Recommended with restrictions

▶ Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (July 2018) NICE TA529 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Crizotinib (Xalkori ®) for treatment of adults with ROS1-positive advanced non-small cell lung cancer (June 2018) SMC No. 1329/18 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

▶ Xalkori (Pfizer Ltd)

Crizotinib 200 mg Xalkori 200mg capsules | 60 capsule^{P} £4,689.00 (Hospital only)

Crizotinib 250 mg Xalkori 250mg capsules | 60 capsule^{P} £4,689.00 (Hospital only)

Dabrafenib 21-Aug-2020

ı DRUG ACTION Dabrafenib is a BRAF kinase inhibitor, which inhibits BRAF V600 mutation-positive melanoma cell growth.

ı INDICATIONS AND DOSE

Unresectable or metastatic melanoma with a BRAF V600 mutation (as monotherapy or in combination with trametinib) (specialist use only) | Advanced non-small cell lung cancer with a BRAF V600 mutation (in combination with trametinib) (specialist use only)

▶ BY MOUTH

▶ Adult: 150 mg every 12 hours, for dose adjustments due to side-effects, consult product literature

Adjuvant treatment of stage III melanoma with a BRAF V600 mutation following complete resection (in combination with trametinib) (specialist use only)

▶ BY MOUTH

▶ Adult: 150 mg every 12 hours for 12 months, for dose adjustments due to side-effects, consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı CONTRA-INDICATIONS BRAF wild-type melanoma . BRAF wild-type non-small cell lung cancer

ı CAUTIONS Elderly (more frequent dose adjustments may be required) . prior or concurrent cancer associated with RAS mutations—risk of secondary or recurrent malignancy

ı INTERACTIONS → Appendix 1: dabrafenib

ı SIDE-EFFECTS

▶ Common or very common Alopecia . appetite decreased . arthralgia . asthenia . chills . constipation . cough . diarrhoea . fever . headache . hyperglycaemia . hypophosphataemia . influenza like illness . myalgia . nausea . neoplasms . pain in extremity . photosensitivity reaction . skin reactions . vomiting

▶ Uncommon Nephritis . pancreatitis . panniculitis . renal impairment . uveitis

SIDE-EFFECTS, FURTHER INFORMATION Additional sideeffects reported when used in combination with trametinib include dizziness, hyperhidrosis, hyponatraemia, hypotension, leucopenia, muscle spasms, myocarditis, neutropenia, night sweats, and thrombocytopenia.

I CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective non-hormonal contraception during and for 4 weeks after stopping treatment.

I PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment—no information available.

I RENAL IMPAIRMENT Manufacturer advises caution in severe impairment—no information available.

I MONITORING REQUIREMENTS Manufacturer advises assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, monthly during treatment, and for 6 months after discontinuation or until initiation of alternative treatment; assess and monitor for noncutaneous secondary or recurrent malignancy before, during, and for 6 months after discontinuation or until initiation of alternative treatment—consult product literature; monitor full blood count as clinically indicated; monitor for ophthalmologic reactions including uveitis, iridocyclitis and iritis; monitor serum creatinine.

I PATIENT AND CARER ADVICE Manufacturer advises patients should be informed to immediately report new skin lesions—risk of cutaneous squamous cell carcinoma and new primary melanoma.

Missed doses Manufacturer advises if a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of ocular adverse reactions.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (October 2014) NICE TA321 Recommended with restrictions

▶ Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (June 2016) NICE TA396 Recommended with restrictions

▶ Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (October 2018) NICE TA544 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Dabrafenib (Tafinlar ◆) for the monotherapy of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (March 2015) SMC No. 1023/15 Recommended with restrictions

▶ Dabrafenib (Tafinlar ◆) in combination with trametinib for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection (February 2019) SMC No. SMC2131 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 3, 23, 25

▶ Tafinlar (Novartis Pharmaceuticals UK Ltd)

Dabrafenib (as Dabrafenib mesilate) 50 mg Tafinlar 50mg capsules | 28 capsule^{P} £933.33 (Hospital only)

Dabrafenib (as Dabrafenib mesilate) 75 mg Tafinlar 75mg capsules | 28 capsule^{P} £1,400.00 (Hospital only)

Dacomitinib 31-Aug-2020

I DRUG ACTION Dacomitinib is a tyrosine kinase inhibitor that inhibits epidermal growth factor receptor (EGFR).

I INDICATIONS AND DOSE

Non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations (specialist use only)

▶ BY MOUTH

▶ Adult: 45 mg once daily, for dose adjustments, treatment interruption or discontinuation due to sideeffects—consult product literature

I INTERACTIONS → Appendix 1: dacomitinib

I SIDE-EFFECTS

▶ Common or very common Alopecia . appetite decreased . asthenia . dehydration . diarrhoea . dry eye . dry mouth . eye inflammation . hypertrichosis . hypokalaemia . increased risk of infection . interstitial lung disease (discontinue permanently) . mucositis . nail discolouration . nail disorders . nausea . oral disorders . oropharyngeal pain . pneumonitis (discontinue permanently) . skin reactions . taste altered . vomiting . weight decreased

I CONCEPTION AND CONTRACEPTION Manufacturer advises females of childbearing potential should use effective contraception during treatment and for at least 17 days after stopping treatment.

I PREGNANCY Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment (no information available).

I RENAL IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).

I MONITORING REQUIREMENTS Manufacturer advises monitor liver function periodically—interrupt treatment if severe changes in liver function occur.

I PATIENT AND CARER ADVICE

Photosensitivity Manufacturer advises patients should wear protective clothing and apply sunscreen before sun exposure.

Driving and skilled tasks Manufacturer advises patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of fatigue and ocular side-effects.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Dacomitinib for untreated EGFR mutation-positive non-small cell lung cancer (August 2019) NICE TA595 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Dacomitinib (Vizimpro ®) as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations (September 2019) SMC No. SMC2184 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Vizimpro (Pfizer Ltd) A

Dacomitinib (as Dacomitinib monohydrate) 15 mg Vizimpro 15mg tablets | 30 tabletP £2,703.00 (Hospital only)

Dacomitinib (as Dacomitinib monohydrate) 30 mg Vizimpro 30mg tablets | 30 tabletP £2,703.00 (Hospital only)

Dacomitinib (as Dacomitinib monohydrate) 45 mg Vizimpro 45mg tablets | 30 tabletP £2,703.00 (Hospital only)

Dasatinib 24-Nov-2020

I DRUG ACTION Dasatinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Chronic phase chronic myeloid leukaemia (initiated by a specialist)

▶ BY MOUTH USING TABLETS

▶ Adult: 100 mg once daily, then increased if necessary up to 140 mg once daily, for dose adjustment due to side-effects—consult product literature

▶ BY MOUTH USING ORAL SUSPENSION

▶ Adult (body-weight 30–44 kg): 105 mg once daily, adjust dose based on changes in body-weight every 3 months or more often if necessary; for dose escalation, or dose adjustment due to side-effects—consult product literature

▶ Adult (body-weight 45 kg and above): 120 mg once daily, adjust dose based on changes in body-weight every 3 months or more often if necessary; for dose escalation, or dose adjustment due to side-effects—consult product literature

Accelerated and blast phase chronic myeloid leukaemia [resistant or intolerant to prior therapy] (initiated by a specialist) | Acute lymphoblastic leukaemia [resistant or intolerant to prior therapy] (initiated by a specialist)

▶ BY MOUTH USING TABLETS

▶ Adult: 140 mg once daily, then increased if necessary up to 180 mg once daily, for dose adjustment due to side-effects—consult product literature

DOSE EQUIVALENCE AND CONVERSION

▶ Sprycel ⋆ film-coated tablets and Sprycel ⋆ powder for oral suspension are not bioequivalent. Follow correct dosing recommendations for the dosage form when switching formulations.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS

An EU wide review has concluded that dasatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

ı CAUTIONS Hepatitis B infection . risk of cardiac dysfunction (monitor closely) . susceptibility to QTinterval prolongation (correct hypokalaemia or hypomagnesaemia before starting treatment)

CAUTIONS, FURTHER INFORMATION

▶ Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

ı INTERACTIONS → Appendix 1: dasatinib

ı SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite abnormal . arrhythmias . arthralgia . asthenia . bone marrow depression . cardiac disorder . cardiomyopathy . chest pain . chills . constipation . cough . depression . diarrhoea . dizziness . drowsiness . dry eye . dyspnoea . eye inflammation . facial swelling . fever . fluid imbalance . flushing . gastrointestinal discomfort . gastrointestinal disorders . genital abnormalities . haemorrhage . headache . heart failure . hypertension . hyperuricaemia . increased risk of infection . insomnia . milia . mucositis . muscle complaints . muscle weakness . musculoskeletal stiffness .

myocardial dysfunction . nausea . nerve disorders . neutropenia . oedema . oral disorders . pain . palpitations . pericardial effusion . perinephric effusion . peripheral swelling . pulmonary hypertension . pulmonary oedema . respiratory disorders . sepsis . skin reactions . sweat changes . taste altered . thrombocytopenia . tinnitus . vision disorders . vomiting . weight changes

▶ Uncommon Acute coronary syndrome . anxiety . arthritis . ascites . asthma . cardiac inflammation . cardiomegaly . cerebrovascular insufficiency . cholecystitis . CNS haemorrhage . confusion . dysphagia . embolism and thrombosis . emotional lability . excessive tearing . gynaecomastia . hair disorder . hearing loss . hepatic disorders . hypercholesterolaemia . hypoalbuminaemia . hypotension . hypothyroidism . ischaemic heart disease . libido decreased . lymphadenopathy . lymphopenia . malaise . memory loss . menstrual disorder . movement disorders . myopathy . nail disorder . osteonecrosis . pancreatitis . panniculitis . penile disorders . photosensitivity reaction . proteinuria .QT interval prolongation . renal impairment . scrotal oedema . skin ulcer . syncope . tendinitis . testicular swelling . tremor . tumour lysis syndrome . urinary frequency increased . vertigo . vulvovaginal swelling

▶ Rare or very rare Cardiac arrest . dementia . diabetes mellitus . epiphyses delayed fusion . facial paralysis . gait abnormal . growth retardation . hypersensitivity vasculitis . hyperthyroidism . pure red cell aplasia . seizure . thyroiditis

▶ Frequency not known Hepatitis B reactivation . nephrotic

syndrome . Stevens-Johnson syndrome . thrombotic microangiopathy

ı CONCEPTION AND CONTRACEPTION Effective contraception required during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı HEPATIC IMPAIRMENT Manufacturer advises caution.

ı MONITORING REQUIREMENTS

▶ Manufacturer advises evaluate for signs and symptoms of underlying cardiopulmonary disease before initiation of therapy—echocardiography should be performed at treatment initiation in patients with symptoms of cardiac disease and considered for patients with risk factors for cardiac or pulmonary disease.

▶ Manufacturer advises monitor patients with risk factors or a history of cardiac disease for signs or symptoms of cardiac dysfunction during treatment.

▶ When used for Accelerated or blast phase chronic myeloid leukaemia or Acute lymphoblastic leukaemia Manufacturer advises monitor full blood count weekly for the first 2 months, then monthly or as clinically indicated thereafter.

▶ When used for Chronic phase chronic myeloid leukaemia Manufacturer advises monitor full blood count every 2 weeks for 3 months, then every 3 months or as clinically indicated thereafter.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA426 Recommended with restrictions

▶ Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Dasatinib (Sprycel ®) tablets for the treatment of adult patients with chronic, accelerated or blast phase chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate (September 2016) SMC No. 370/07 Recommended

▶ Dasatinib (Sprycel ®) tablets for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase (September 2016) SMC No. 1170/16 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral suspension

EXCIPIENTS: May contain Benzyl alcohol, sucrose

▶ Sprycel (Bristol-Myers Squibb Pharmaceuticals Ltd)

Dasatinib (as Dasatinib monohydrate) 10 mg per 1 ml Sprycel 10mg/ml oral suspension | 99 ml P £626.74

Tablet

CAUTIONARY AND ADVISORY LABELS 25

▶ Dasatinib (Non-proprietary)

Dasatinib (as Dasatinib monohydrate) 20 mg Dasatinib 20mg tablets | 60 tablet P £650.00 DT = £1,252.48

Dasatinib (as Dasatinib monohydrate) 50 mg Dasatinib 50mg tablets | 60 tablet P £1,200.00 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 80 mg Dasatinib 80mg tablets | 30 tablet P £1,200.00 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 100 mg Dasatinib 100mg tablets | 30 tablet P £1,200.00 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 140 mg Dasatinib 140mg tablets | 30 tablet P £1,200.00 DT = £2,504.96

▶ Sprycel (Bristol-Myers Squibb Pharmaceuticals Ltd)

Dasatinib (as Dasatinib monohydrate) 20 mg Sprycel 20mg tablets | 60 tablet P £1,252.48 DT = £1,252.48

Dasatinib (as Dasatinib monohydrate) 50 mg Sprycel 50mg tablets | 60 tablet P £2,504.96 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 80 mg Sprycel 80mg tablets | 30 tablet P £2,504.96 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 100 mg Sprycel 100mg tablets | 30 tablet P £2,504.96 DT = £2,504.96

Dasatinib (as Dasatinib monohydrate) 140 mg Sprycel 140mg tablets | 30 tablet P £2,504.96 DT = £2,504.96

Encorafenib 28-May-2021

ı DRUG ACTION Encorafenib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically BRAF kinase, thereby inhibiting BRAF V600 mutation-positive cell

growth.

INDICATIONS AND DOSE

Unresectable or metastatic melanoma with a BRAF V600 mutation (in combination with binimetinib) (specialist use only)

▶ BY MOUTH

▶ Adult: 450 mg once daily, for dose adjustments due to side-effects, consult product literature

Metastatic colorectal cancer with a BRAF V600E mutation (in combination with cetuximab) (specialist use only)

▶ BY MOUTH

▶ Adult: 300 mg once daily, for dose adjustments due to side-effects, consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CONTRA-INDICATIONS BRAF wild-type colorectal cancer . BRAF wild-type malignant melanoma

CAUTIONS Prior or concurrent cancer associated with RAS mutation . risk factors for QT-interval prolongation

INTERACTIONS → Appendix 1: encorafenib

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . angioedema . appetite decreased . arrhythmias . arthralgia . arthritis . constipation . detachment of retinal pigment epithelium . diarrhoea . dizziness . embolism and thrombosis . eye inflammation . facial paralysis . fatigue . fever . fluid retention . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . heart failure . hypersensitivity . hypersensitivity vasculitis . hypertension . insomnia . intracranial haemorrhage . left ventricular dysfunction . lip squamous cell carcinoma . muscle complaints . muscle weakness . myopathy . nausea . neoplasms . nerve disorders . oedema . pain . panniculitis . paresis . photosensitivity reaction . renal impairment . skin reactions . taste altered . ulcerative colitis . vision disorders . vomiting

▶ Uncommon Pancreatitis

▶ Frequency not known QT interval prolongation

CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use effective contraception during and for at least one month after stopping treatment; additional barrier method recommended in women using hormonal contraceptives.

PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution in mild impairment (increased exposure); avoid in moderate or severe impairment (no information available).

Dose adjustments Manufacturer advises dose reduction to 300mg once daily in mild impairment.

RENAL IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).

MONITORING REQUIREMENTS

▶ Manufacturer advises assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, every 2 months during treatment, and for up to 6 months after discontinuation; assess for non-cutaneous malignancy and monitor full blood count before, during, and after treatment discontinuation as clinically indicated—consult product literature.

▶ Manufacturer advises monitor liver function before treatment, at least monthly during the first 6 months, and thereafter as clinically indicated.

▶ Manufacturer advises assess ECG before treatment, one month after starting treatment, then every 3 months or more frequently as clinically indicated.

▶ Manufacturer advises monitor blood creatinine levels as clinically indicated.

▶ Manufacturer advises monitor for ophthalmologic reactions including uveitis, iridocyclitis, and iritis.

PATIENT AND CARER ADVICE Manufacturer advises

patients should be informed to immediately report new skin lesions—risk of cutaneous squamous cell carcinoma and new primary melanoma.
Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of visual disturbances.

I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma (February 2019) NICE TA562 Recommended with restrictions
▶ Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer (January 2021) NICE TA668 Recommended
Scottish Medicines Consortium (SMC) decisions
▶ Encorafenib (Braftovi ∗) in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (February 2020) SMC No. SMC2238 Recommended
▶ Encorafenib (Braftovi ∗) in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy (May 2021) SMC No. SMC2312 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Capsule
CAUTIONARY AND ADVISORY LABELS 3, 25
▶ Braftovi (Pierre Fabre Ltd) A
Encorafenib 50 mg Braftovi 50mg capsules | 28 capsuleP
£622.22 (Hospital only)
Encorafenib 75 mg Braftovi 75mg capsules | 42 capsuleP
£1,400.00 (Hospital only)

Entrectinib 30-Mar-2021

I DRUG ACTION Entrectinib is a tropomyosin receptor kinase inhibitor.

I INDICATIONS AND DOSE
Solid tumours with neurotrophic tyrosine receptor kinase gene fusion (initiated by a specialist)
▶ BY MOUTH
▶ Adult: 600 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature
ROS1-positive advanced non-small cell lung cancer (initiated by a specialist)
▶ BY MOUTH
▶ Adult: 600 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce entrectinib dose to 100mg once daily; if concomitant use with moderate CYP3A4 inhibitors is unavoidable, reduce entrectinib dose to 200mg once daily.

I CONTRA-INDICATIONS Congenital long QT syndrome

I CAUTIONS Susceptibility to QT-interval prolongation . symptoms or risk factors for congestive heart failure (assess left ventricular ejection fraction before initiation)

CAUTIONS, FURTHER INFORMATION
▶ QT-interval prolongation QT-interval prolongation has been observed in clinical studies. Manufacturer advises avoid in patients with pre-existing risk factors; if potential benefit outweighs risk in this patient group, additional monitoring should be considered. Monitor ECG and electrolytes in all patients before treatment, after 1 month, and periodically as clinically indicated (treatment not recommended if QT interval greater than 450 milliseconds at baseline)—consult product literature if QT-interval prolongation occurs during treatment.

I INTERACTIONS → Appendix 1: entrectinib

I SIDE-EFFECTS
▶ Common or very common Abdominal pain . anaemia . anxiety . appetite decreased . arthralgia . asthenia . bone fractures . cognitive disorder . concentration impaired . confusion . constipation . cough . delirium . depression . diarrhoea . dizziness . drowsiness . dysphagia . dyspnoea . fever . fluid imbalance . gait abnormal . hallucinations .

headache . heart failure . hyperuricaemia . hypotension . increased risk of infection . memory impairment . mood altered . movement disorders . muscle weakness . myalgia . nausea . neutropenia . oedema . pain . peripheral neuropathy . peripheral swelling . photosensitivity reaction . pleural effusion . psychiatric disorders . pulmonary oedema .QT interval prolongation . sensation abnormal . skin reactions . sleep disorders . syncope . taste altered . urinary disorders . vertigo . vision disorders . vomiting . weight increased

▶ Uncommon Tumour lysis syndrome

ı CONCEPTION AND CONTRACEPTION Manufacturer advises females of childbearing potential should use effective contraception during treatment and for 5 weeks after last treatment; male patients should use effective contraception during treatment and for 3 months after last treatment if their partner is of childbearing potential. Additional barrier method recommended in females using hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid—limited information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—no information available.

ı PATIENT AND CARER ADVICE

Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. If vomiting occurs immediately after a dose is taken, patients may repeat the dose.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of cognitive disorders, syncope, blurred vision, or dizziness.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer (August 2020) NICE TA643 Recommended

▶ Entrectinib for treating NTRK fusion-positive solid tumours (August 2020) NICE TA644 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Entrectinib (Rozlytrek ®) for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS-1 inhibitors (January 2021) SMC No. SMC2294 Recommended

▶ Entrectinib (Rozlytrek ®) for the treatment of adult and paediatric patients 12 years of age and older,with solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion (March 2021) SMC No. SMC2295 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

▶ Rozlytrek (Roche Products Ltd) A

Entrectinib 100 mg Rozlytrek 100mg capsules | 30 capsuleP £860.00 (Hospital only)

Entrectinib 200 mg Rozlytrek 200mg capsules | 90 capsuleP £5,160.00 (Hospital only)

Erlotinib 18-May-2021

ı DRUG ACTION Erlotinib is a tyrosine kinase inhibitor.

ı INDICATIONS AND DOSE

Treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy | Monotherapy for maintenance treatment of locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of platinum-based chemotherapy

▶ BY MOUTH

▶ Adult: 150 mg once daily

Treatment of metastatic pancreatic cancer (in combination with gemcitabine)

▶ BY MOUTH

▶ Adult: 100 mg once daily

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concurrent use of potent inducers of CYP3A4 is unavoidable, increase dose to 300mg daily, if well tolerated for more than 2 weeks,

further increase to 450mg daily could be considered with close monitoring.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CAUTIONS

▶ Smoking Dose adjustment may be necessary if smoking started or stopped during treatment.

INTERACTIONS → Appendix 1: erlotinib

SIDE-EFFECTS

▶ Common or very common Alopecia . diarrhoea . eye inflammation . haemorrhage . increased risk of infection . renal failure . skin reactions

▶ Uncommon Brittle nails . eye disorders . gastrointestinal disorders . hair changes . interstitial lung disease . nephritis . proteinuria

▶ Rare or very rare Hepatic failure . severe cutaneous adverse reactions (SCARs)

▶ Frequency not known Appetite decreased . chills . cough . depression . dyspnoea . fatigue . fever . gastrointestinal discomfort . headache . nausea . neuropathy sensory . stomatitis . vomiting . weight decreased

CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 2 weeks after treatment.

PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid breastfeeding during treatment and for at least 2 weeks after the last dose.

HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment—monitor liver function and

interrupt treatment if changes in liver function are severe (increased risk of hepatic failure); avoid in severe impairment—no information available.

Dose adjustments Manufacturer advises consider dose reduction or interruption if serious adverse effects occur.

RENAL IMPAIRMENT Manufacturer advises avoid in severe impairment.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Erlotinib monotherapy for maintenance treatment of nonsmall-cell lung cancer (June 2011) NICE TA227 Not recommended

▶ Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (June 2012) NICE TA258 Recommended with restrictions

▶ Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy [in patients with tumours that are EGFR-TK mutation-negative] (December 2015) NICE TA374 Not recommended

▶ Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy [in patients with tumours of unknown EGFR-TK mutation status] (December 2015) NICE TA374 Recommended with restrictions

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 23

▶ Erlotinib (Non-proprietary)

Erlotinib (as Erlotinib hydrochloride) 25 mg Erlotinib 25mg tablets | 30 tablet$_P$ £88.40–£321.58 | 30 tablet$_P$ £139.00–£378.33 (Hospital only)

Erlotinib (as Erlotinib hydrochloride) 100 mg Erlotinib 100mg tablets | 30 tablet$P £418.20–£1,125.52 | 30 tablet$P £378.33–£704.00 (Hospital only)
Erlotinib (as Erlotinib hydrochloride) 150 mg Erlotinib 150mg tablets | 30 tablet$P £489.08–£1,386.80 | 30 tablet$P £378.33–£815.00 (Hospital only)
▶ Tarceva (Roche Products Ltd)
Erlotinib (as Erlotinib hydrochloride) 25 mg Tarceva 25mg tablets | 30 tablet$P £378.33
Erlotinib (as Erlotinib hydrochloride) 100 mg Tarceva 100mg tablets | 30 tablet$P £1,324.14
Erlotinib (as Erlotinib hydrochloride) 150 mg Tarceva 150mg tablets | 30 tablet$P £1,631.53

Everolimus 25-Oct-2021

DRUG ACTION Everolimus is a protein kinase inhibitor.

INDICATIONS AND DOSE

Neuroendocrine tumours of pancreatic origin | Neuroendocrine tumours of gastro-intestinal origin

▶ BY MOUTH

▶ Adult: 10 mg once daily, for dose interruption or adjustments due to side effects—consult product literature

AFINITOR •

Neuroendocrine tumours of pancreatic origin | Neuroendocrine tumours of lung origin | Neuroendocrine tumours of gastro-intestinal origin | Renal cell carcinoma | Hormone-receptor positive HER2-negative breast cancer [in combination with exemestane]

▶ BY MOUTH

▶ Adult: 10 mg once daily, for dose interruption or adjustments due to side-effects—consult product literature

CERTICAN •

Liver transplantation

▶ BY MOUTH

▶ Adult: Initially 1 mg twice daily, to be started approximately 4 weeks after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Renal transplantation | Heart transplantation

▶ BY MOUTH

▶ Adult: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance, dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

VOTUBIA • DISPERSIBLE TABLETS

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

▶ BY MOUTH USING DISPERSIBLE TABLETS

▶ Adult: (consult product literature)

Adjunctive treatment of refractory partial-onset seizures, with or without secondary generalisation, associated with tuberous sclerosis complex

▶ BY MOUTH USING DISPERSIBLE TABLETS

▶ Adult: (consult product literature)

VOTUBIA • TABLETS

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

▶ BY MOUTH USING TABLETS

▶ Adult: (consult product literature)

Renal angiomyolipoma associated with tuberous sclerosis complex

▶ BY MOUTH USING TABLETS

▶ Adult: (consult product literature)

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE: ANTIEPILEPTICS: RISK OF SUICIDAL THOUGHTS AND BEHAVIOUR (AUGUST 2008)

See Epilepsy p. 330.

MHRA/CHM ADVICE: ANTIEPILEPTIC DRUGS: UPDATED ADVICE ON SWITCHING BETWEEN DIFFERENT MANUFACTURERS' PRODUCTS (NOVEMBER 2017)

See Epilepsy p. 330 and see also Prescribing and dispensing information.

MHRA/CHM ADVICE: ANTIEPILEPTIC DRUGS IN PREGNANCY: UPDATED ADVICE FOLLOWING COMPREHENSIVE SAFETY REVIEW (JANUARY 2021)

See Epilepsy p. 330.

CAUTIONS History of bleeding disorders . peri-surgical period (impaired wound healing)

INTERACTIONS → Appendix 1: everolimus

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite

decreased . arthralgia . asthenia . cough . decreased leucocytes . dehydration . diabetes mellitus . diarrhoea . dry mouth . dyslipidaemia . dysphagia . dyspnoea . electrolyte imbalance . eye inflammation . fever . gastrointestinal discomfort . haemorrhage . headache . hyperglycaemia . hypertension . increased risk of infection . insomnia . menstrual cycle irregularities . mucositis . nail disorders . nausea . neutropenia . oral disorders . peripheral oedema . proteinuria . renal impairment . respiratory disorders . skin reactions . taste altered . thrombocytopenia . vomiting . weight decreased

▶ Uncommon Congestive heart failure . embolism and thrombosis . flushing . healing impaired . hepatitis B .

musculoskeletal chest pain . pancytopenia . sepsis . urinary frequency increased

▶ Rare or very rare Pure red cell aplasia

▶ Frequency not known Hepatitis B reactivation . suicidal behaviours

SIDE-EFFECTS, FURTHER INFORMATION Reduce dose or discontinue if severe side-effects occur—consult product literature.

CONCEPTION AND CONTRACEPTION Effective contraception must be used during and for up to 8 weeks after treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. See also Pregnancy in Epilepsy p. 330.

BREAST FEEDING Manufacturer advises avoid.

HEPATIC IMPAIRMENT Consult product literature.

MONITORING REQUIREMENTS

▶ For Votubia ◆ preparations: manufacturer advises everolimus blood concentration monitoring is required—consult product literature.

▶ For Certican ◆: manufacturer advises pre-dose ('trough') whole blood everolimus concentration should be 3–8 nanograms/mL; monitoring should be performed every 4–5 days (using chromatographic assay) after initiation or dose adjustment until 2 consecutive stable concentrations; monitor patients with hepatic impairment taking concomitant strong CYP3A4 inducers and inhibitors when switching formulation, and/or if concomitant ciclosporin dose is reduced.

▶ Manufacturer advises monitor blood-glucose concentration, complete blood count, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter.

▶ Manufacturer advises monitor renal function before treatment and periodically thereafter.

▶ Manufacturer advises monitor for signs and symptoms of infection before and during treatment.

DIRECTIONS FOR ADMINISTRATION

VOTUBIA ◆ DISPERSIBLE TABLETS Manufacturer advises tablets must be dispersed in water before administration—consult product literature for details.

VOTUBIA ◆ TABLETS Manufacturer advises tablets may be dispersed in approximately 30mL of water by gently stirring, immediately before drinking. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed.

PRESCRIBING AND DISPENSING INFORMATION Votubia ◆ is available as both tablets and dispersible tablets. These formulations vary in their licensed indications and are not interchangeable—consult product literature for information on switching between formulations.

PATIENT AND CARER ADVICE

Pneumonitis Non-infectious pneumonitis reported. Manufacturer advises patients and their carers should be informed to seek urgent medical advice if new or worsening respiratory symptoms occur.

Infections Manufacturer advises patients and their carers should be informed of the risk of infection.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Everolimus with exemestane for treating advanced breast

cancer after endocrine therapy (December 2016) NICE TA421 Recommended with restrictions
▶ Everolimus for advanced renal cell carcinoma after previous treatment (February 2017) NICE TA432 Recommended with restrictions
▶ Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (June 2017) NICE TA449 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Everolimus dispersible tablets (Votubia ∗) for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (June 2018) SMC No. 1331/18 Recommended
All Wales Medicines Strategy Group (AWMSG) decisions
▶ Everolimus dispersible tablets (Votubia ∗) for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC) (September 2021) AWMSG No. 2142 Recommended
AFINITOR ∗ For full details see funding body website
NICE decisions
▶ Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (January 2018) NICE TA498 Recommended with restrictions
CERTICAN ∗ For full details see funding body website
NICE decisions
▶ Everolimus for preventing organ rejection in liver transplantation (July 2015) NICE TA348 Not recommended
▶ Immunosuppressive therapy for kidney transplant in adults (October 2017) NICE TA481 Not recommended
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Dispersible tablet
CAUTIONARY AND ADVISORY LABELS 13
▶ Votubia (Novartis Pharmaceuticals UK Ltd)
Everolimus 2 mg Votubia 2mg dispersible tablets sugar-free | 30 tabletP £960.00
Everolimus 3 mg Votubia 3mg dispersible tablets sugar-free | 30 tabletP £1,440.00
Everolimus 5 mg Votubia 5mg dispersible tablets sugar-free | 30 tabletP £2,250.00
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Everolimus (Non-proprietary)
Everolimus 2.5 mg Everolimus 2.5mg tablets | 30 tabletP £1,020.00–£1,200.00 | 30 tabletP £1,200.00 (Hospital only)
Everolimus 5 mg Everolimus 5mg tablets | 30 tabletP £1,912.50–£2,250.00 | 30 tabletP £2,250.00 (Hospital only)
Everolimus 10 mg Everolimus 10mg tablets | 30 tabletP £2,272.05–£2,673.00 | 30 tabletP £2,405.70–£2,673.00 (Hospital only)
▶ Afinitor (Novartis Pharmaceuticals UK Ltd)
Everolimus 2.5 mg Afinitor 2.5mg tablets | 30 tabletP £1,200.00
Everolimus 5 mg Afinitor 5mg tablets | 30 tabletP £2,250.00
Everolimus 10 mg Afinitor 10mg tablets | 30 tabletP £2,673.00
▶ Certican (Novartis Pharmaceuticals UK Ltd)
Everolimus 250 microgram Certican 0.25mg tablets | 60 tabletP £148.50
Everolimus 750 microgram Certican 0.75mg tablets | 60 tabletP £445.20
▶ Votubia (Novartis Pharmaceuticals UK Ltd)
Everolimus 2.5 mg Votubia 2.5mg tablets | 30 tabletP £1,200.00
Everolimus 5 mg Votubia 5mg tablets | 30 tabletP £2,250.00
Everolimus 10 mg Votubia 10mg tablets | 30 tabletP £2,970.00

Fedratinib 04-May-2022

I DRUG ACTION Fedratinib is a kinase inhibitor with activity against Janus-associated tyrosine kinase JAK2 and FMSlike tyrosine kinase FLT3, thereby reducing the abnormal production of blood cells and associated symptoms.
I INDICATIONS AND DOSE
Disease-related splenomegaly or symptoms [in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis] (specialist use only)
▶ BY MOUTH
▶ Adult: 400 mg once daily, for dose reduction, interruption, or discontinuation due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ gIf concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce fedratinib dose to 200mg once daily and monitor patients weekly for side-effects. If the potent CYP3A4 inhibitor is stopped, increase the dose to 300mg once daily for two weeks, then to 400mg once daily thereafter. M
I CONTRA-INDICATIONS Absolute neutrophil count less than $1x10^9$ cells/litre (do not initiate) . platelet count less than $50x10^9$/litre (do not initiate) . thiamine deficiency
I CAUTIONS Patients 75 years of age or older (increased incidence of side-effects—limited information available)
I INTERACTIONS → Appendix 1: fedratinib
I SIDE-EFFECTS
▶ Common or very common Anaemia . asthenia . constipation . diarrhoea . dizziness . dyspepsia . dysuria . haemorrhage . headache . hypertension . muscle spasms . nausea . neutropenia . pain . thrombocytopenia . urinary tract infection . vomiting . weight increased . Wernicke's encephalopathy
▶ Frequency not known Hepatic failure . pancreatitis
SIDE-EFFECTS, FURTHER INFORMATION Nausea is very common, often occurring within 2 days of starting treatment. Nausea can be managed by prescribing concurrent antiemetics (consult product literature), and/or taking doses with a high fat meal.
I CONCEPTION AND CONTRACEPTION gFemales of childbearing potential should use effective contraception during treatment and for at least 1 month after last treatment. M
I PREGNANCY gAvoid—toxicity in animal studies. M
I BREAST FEEDING gAvoid during treatment and for at least 1 month after last treatment. M
I HEPATIC IMPAIRMENT gAvoid in severe impairment (no information available). M
I RENAL IMPAIRMENT gCaution in moderate and severe impairment (creatinine clearance less than 59 mL/minute); monitor at least weekly and consider dose adjustment if side-effects occur (risk of increased exposure)—consult product literature. M
Dose adjustments gReduce dose to 200mg once daily in severe impairment (creatinine clearance 15–29 mL/minute). MSee p. 21.
I MONITORING REQUIREMENTS
▶gMonitor transaminases, serum creatinine, amylase, and lipase levels before treatment initiation, then monthly for the first 3 months and periodically during treatment, and as clinically indicated. Monitor patients every 2 weeks until resolution if levels are elevated.
▶ Monitor full blood count and blood urea nitrogen levels before treatment initiation, periodically during treatment, and as clinically indicated.
▶ Patients with haemoglobin less than 10 g/dL or platelet count less than $100x10^9$/litre at the start of treatment should be monitored weekly for the first month until levels improve.
▶ Monitor thiamine levels and nutritional status before treatment initiation, then monthly for the first 3 months and then every 3 months thereafter, and as clinically indicated. Correct thiamine levels if low before or during treatment. M
I PATIENT AND CARER ADVICE
Driving and skilled tasks Patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (December 2021) NICE TA756 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Fedratinib (Inrebic ®) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or postessential thrombocythaemia myelofibrosis who are Janusassociated kinase inhibitor-naive or who have been treated with ruxolitinib (April 2022) SMC No. SMC2462 Recommended
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Capsule
CAUTIONARY AND ADVISORY LABELS 25
▶ Inrebic (Bristol-Myers Squibb Pharmaceuticals Ltd) A

Fedratinib (as Fedratinib dihydrochloride monohydrate) 100 mg Inrebic 100mg capsules | 120 capsule^{P} £6,119.68 (Hospital only)

Gefitinib 19-Jul-2021

I DRUG ACTION Gefitinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor

▶ BY MOUTH

▶ Adult: 250 mg once daily

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I INTERACTIONS → Appendix 1: gefitinib

I SIDE-EFFECTS

▶ Common or very common Alopecia . angioedema . appetite decreased . asthenia . cystitis . dehydration . diarrhoea . dry eye . dry mouth . eye inflammation . fever . haemorrhage . hypersensitivity . interstitial lung disease (discontinue) .

nail disorder . nausea . proteinuria . rash pustular . skin reactions . stomatitis . vomiting

▶ Uncommon Corneal erosion . gastrointestinal perforation . hepatic disorders . pancreatitis

▶ Rare or very rare Cutaneous vasculitis . severe cutaneous adverse reactions (SCARs)

I CONCEPTION AND CONTRACEPTION Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Discontinue breast-feeding.

I HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment due to cirrhosis—monitor for adverse events (risk of increased drug plasma concentrations).

I RENAL IMPAIRMENT gUse with caution if creatinine clearance less than 20 mL/minute (limited information available), Msee p. 21.

I MONITORING REQUIREMENTS

▶ Monitor for worsening of dyspnoea, cough and fever—discontinue if interstitial lung disease confirmed.

▶ Monitor liver function—consider discontinuing if severe changes in liver function occur.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (July 2010) NICE TA192 Recommended with restrictions

▶ Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (December 2015) NICE TA374 Not recommended

Scottish Medicines Consortium (SMC) decisions

▶ Gefitinib (Iressa ®) for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor tyrosine kinase (December 2015) SMC No. 615/10 Recommended with restrictions

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Gefitinib (Non-proprietary)

Gefitinib 250 mg Gefitinib 250mg tablets | 30 tablet^{P}

£1,500.00–£2,167.71 | 30 tablet℗ £1,781.94 (Hospital only)
▶ Iressa (AstraZeneca UK Ltd)
Gefitinib 250 mg Iressa 250mg tablets | 30 tablet℗ £2,167.71

Gilteritinib 06-Nov-2020

ı DRUG ACTION Gilteritinib is a FMS-like tyrosine kinase-3 (FLT3) inhibitor.

ı INDICATIONS AND DOSE

FLT3 mutation-positive acute myeloid leukaemia (specialist use only)

▶ BY MOUTH

▶ Adult: 120 mg once daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature, if no response is observed after 4 weeks, dose may be increased to 200mg once daily. Up to 6 months treatment may be required before a clinical response is seen

ı CAUTIONS Risk factors for QT-interval prolongation (including hypokalaemia or hypomagnesaemia)

ı INTERACTIONS → Appendix 1: gilteritinib

ı SIDE-EFFECTS

▶ Common or very common Acute kidney injury . anaphylactic reaction . arthralgia . asthenia . constipation . cough . diarrhoea . differentiation syndrome . dizziness . dyspnoea . heart failure . hypotension . malaise . myalgia . nausea . pain . pericardial effusion . pericarditis . peripheral oedema .QT interval prolongation

▶ Uncommon Posterior reversible encephalopathy syndrome (PRES)

▶ Frequency not known Pancreatitis

ı CONCEPTION AND CONTRACEPTION Manufacturer advises perform pregnancy test in females of childbearing potential within 7 days prior to treatment initiation; effective contraception should be used during treatment and for at least 6 months after last treatment—additional barrier method recommended in those using hormonal contraceptives. Male patients should use effective contraception during treatment and for at least 4 months after last treatment if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises discontinue breast-feeding during treatment and for at least 2 months after stopping—present in milk in animal studies.

ı HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment (no information available).

ı MONITORING REQUIREMENTS

▶ Manufacturer advises monitor blood chemistry, including creatine phosphokinase, before treatment, on day 15 of treatment, and then monthly during treatment.

▶ Manufacturer advises monitor ECG before treatment, on days 8 and 15 of treatment, and then prior to the start of the next three subsequent months of treatment—consult product literature for dose modifications if QT-interval prolonged.

ı PRESCRIBING AND DISPENSING INFORMATION The manufacturer of Xospata ⁎ has provided a Risk minimisation materials document for healthcare professionals.

ı PATIENT AND CARER ADVICE

Vomiting Manufacturer advises if vomiting occurs after taking tablets, no additional dose should be taken on that day and the next dose should be taken at the usual time. A patient alert card should be provided.

Missed doses Manufacturer advises if a dose is missed or not taken at the usual time, the missed dose should be taken as soon as possible on the same day. The next dose should be taken at the usual time.

Driving and skilled tasks Manufacturer advises patients and their carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Gilteritinib for treating relapsed or refractory acute myeloid leukaemia (August 2020) NICE TA642 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Gilteritinib (Xospata ⁎) as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia with a FLT3 mutation (September 2020)

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Xospata (Astellas Pharma Ltd) A
Gilteritinib (as Gilteritinib fumarate) 40 mg Xospata 40mg tablets | 84 tabletP £14,188.00 (Hospital only)

Ibrutinib 18-Jan-2022

I DRUG ACTION Ibrutinib is a tyrosine kinase inhibitor.
I INDICATIONS AND DOSE
Mantle cell lymphoma (specialist use only)
▶ BY MOUTH
▶ Adult: 560 mg once daily, for dose adjustments due to side-effects—consult product literature
Chronic lymphocytic leukaemia (specialist use only) | Waldenström's macroglobulinaemia (specialist use only)
▶ BY MOUTH
▶ Adult: 420 mg once daily, for dose adjustments due to side-effects—consult product literature
DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ Manufacturer advises if concurrent use of moderate inhibitors of CYP3A4, amiodarone or ciprofloxacin is unavoidable, reduce dose to 280mg once daily.
▶ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 140mg once daily, or withhold ibrutinib for up to 7 days.
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
MHRA/CHM ADVICE: IBRUTINIB (IMBRUVICA •): REPORTS OF VENTRICULAR TACHYARRHYTHMIA; RISK OF HEPATITIS B REACTIVATION AND OF OPPORTUNISTIC INFECTIONS (AUGUST 2017)
Cases of ventricular tachyarrhythmia have been reported with the use of ibrutinib. The MHRA advises that ibrutinib should be temporarily discontinued in patients who develop symptoms suggestive of ventricular arrhythmia and to assess benefit-risk before restarting therapy.
Hepatitis B virus status should be established before initiating therapy—for patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before the start of treatment; monitor and manage patients according to local protocols to minimise the risk of hepatitis B virus reactivation. Prophylaxis should be considered for those at an increased risk of opportunistic infections.
I CAUTIONS Family history of congenital short QT syndrome . increased lymphocytes—increased risk of leukostasis, consider withholding treatment temporarily and monitor closely . patients at risk from further shortening of QTc interval . personal history of congenital short QT syndrome . risk of haemorrhagic events—withhold ibrutinib treatment for at least 3 to 7 days before and after surgery depending on risk of bleeding
I INTERACTIONS → Appendix 1: ibrutinib
I SIDE-EFFECTS
▶ Common or very common Arrhythmias . arthralgia . broken nails . CNS haemorrhage . constipation . diarrhoea . dizziness . fever . haemorrhage . headache . hypertension . hyperuricaemia . increased leucocytes . increased risk of infection . interstitial lung disease . muscle spasms . musculoskeletal pain . nausea . neoplasms . neutropenia . peripheral neuropathy . peripheral oedema . sepsis . skin reactions . stomatitis . thrombocytopenia . tumour lysis syndrome . vision blurred . vomiting
▶ Uncommon Angioedema . hepatitis B reactivation . leukostasis syndrome . panniculitis
▶ Frequency not known Anaemia . hepatic failure . progressive multifocal leukoencephalopathy (PML) . Stevens-Johnson syndrome
I CONCEPTION AND CONTRACEPTION Highly effective contraception (must include a non-hormonal method) required during and for 3 months after stopping treatment.

I PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.
I BREAST FEEDING Manufacturer advises discontinue breastfeeding—no information available.
I HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment (risk of increased exposure)—monitor for toxicity.
Dose adjustments Manufacturer advises dose reduction to 280mg daily in mild impairment and to 140mg daily in moderate impairment with further adjustments if necessary–consult product literature.
I RENAL IMPAIRMENT gMaintain adequate hydration in mild to moderate impairment. MgUse in severe impairment only if benefit outweighs risk and with close monitoring for toxicity. M
I MONITORING REQUIREMENTS
▶ Monitor full blood count once a month.
▶ Monitor for atrial fibrillation (increased risk in cardiac risk factors, acute infections and history of atrial fibrillation), monitor all patients periodically and complete ECG if arrhythmic symptoms or dyspnoea develop—consult product literature for treatment options.
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (January 2017) NICE TA429 Recommended with restrictions
▶ Ibrutinib for treating Waldenstrom's macroglobulinaemia (November 2017) NICE TA491 Recommended with restrictions
▶ Ibrutinib for treating relapsed or refractory mantle cell lymphoma (January 2018) NICE TA502 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Ibrutinib (Imbruvica ®) for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy (April 2017) SMC No. 1151/16 Recommended with restrictions
▶ Ibrutinib (Imbruvica ®) in combination with rituximab for the treatment of adult patients with Waldenström's macroglobulinaemia (October 2020) SMC No. SMC2259 Recommended with restrictions
▶ Ibrutinib (Imbruvica ®) as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy (December 2021) SMC No. SMC2387 Recommended with restrictions
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Imbruvica (Janssen-Cilag Ltd)
Ibrutinib 140 mg Imbruvica 140mg tablets | 28 tabletP £1,430.80 (Hospital only)
Ibrutinib 280 mg Imbruvica 280mg tablets | 28 tabletP £2,861.60 (Hospital only)

Ibrutinib 420 mg Imbruvica 420mg tablets | 28 tabletP £4,292.40 (Hospital only)
Ibrutinib 560 mg Imbruvica 560mg tablets | 28 tabletP £5,723.20 (Hospital only)

Idelalisib 16-Oct-2020

I DRUG ACTION Idelalisib is a protein kinase inhibitor.
I INDICATIONS AND DOSE
Treatment of chronic lymphocytic leukaemia in patients who have received at least one previous therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies (in combination with rituximab) | Treatment of follicular lymphoma refractory to two lines of treatment (monotherapy)
▶ BY MOUTH
▶ Adult: 150 mg twice daily, for dose adjustment due to side effects, consult product literature
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
MHRA/CHM ADVICE: IDELALISIB (ZYDELIG®): UPDATED INDICATIONS AND ADVICE ON MINIMISING THE RISK OF INFECTION (SEPTEMBER 2016)
In light of a recent safety review the indications for

idelalisib have been updated. Manufacturer recommendations regarding monitoring for infection and prophylaxis of Pneumocystis jirovecii pneumonia have also been updated. Patients should be advised on the risk of serious or fatal infections during treatment, and idelalisib should not be initiated in patients with any evidence of infection.

CAUTIONS Active hepatitis . diarrhoea—symptomatic management recommended (consult product literature) . pneumonitis—withhold treatment (consult product literature)

INTERACTIONS → Appendix 1: idelalisib

SIDE-EFFECTS

▶ Common or very common Colitis . diarrhoea . fever . infection . neutropenia . pneumonitis . rash

▶ Rare or very rare Severe cutaneous adverse reactions (SCARs)

CONCEPTION AND CONTRACEPTION Highly effective contraception (in addition to barrier method) required during and for one month after treatment.

PREGNANCY Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution (risk of increased exposure-limited information available in severe impairment)—monitor for adverse reactions.

MONITORING REQUIREMENTS

▶ Manufacturer advises monitor liver function—consult product literature.

▶ Manufacturer advises monitor for signs and symptoms of infection, including cytomegalovirus infection and respiratory infections; new symptoms should be reported promptly. Neutrophil count should be monitored in all patients every 2 weeks for the first 6 months of treatment; patients with neutrophil count <1000 per mm^3 should be monitored weekly.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Idelalisib for treating chronic lymphocytic leukaemia (October 2015) NICE TA359 Recommended

▶ Idelalisib for treating refractory follicular lymphoma (October 2019) NICE TA604 Not recommended

Scottish Medicines Consortium (SMC) decisions

▶ Idelalisib (Zydelig ∗) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy (March 2015) SMC No. 1026/15 Recommended with restrictions

▶ Idelalisib (Zydelig ∗) as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment (May 2015) SMC No. 1039/15 Recommended with restrictions

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25

▶ **Zydelig** (Gilead Sciences Ltd)

Idelalisib 100 mg Zydelig 100mg tablets | 60 tablet^{P} £3,114.75 (Hospital only)

Idelalisib 150 mg Zydelig 150mg tablets | 60 tablet^{P} £3,114.75 (Hospital only)

Imatinib 25-Aug-2021

DRUG ACTION Imatinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

▶ BY MOUTH

▶ Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

▶ BY MOUTH

▶ Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy) | Monotherapy for relapsed or refractory acute lymphoblastic leukaemia

▶ BY MOUTH

▶ Adult: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

▶ BY MOUTH

▶ Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protuberans | Recurrent or metastatic dermatofibrosarcoma protuberans, in patients who cannot have surgery

▶ BY MOUTH

▶ Adult: 800 mg daily in 2 divided doses continued→

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

▶ BY MOUTH

▶ Adult: 100–400 mg once daily

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS

An EU wide review has concluded that imatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

ı CAUTIONS Cardiac disease . hepatitis B infection . history of renal failure . risk factors for heart failure

CAUTIONS, FURTHER INFORMATION

▶ Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

ı INTERACTIONS → Appendix 1: imatinib

ı SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite abnormal . asthenia . bone marrow disorders . chills . constipation . cough . diarrhoea . dizziness . dry eye . dry mouth . dyspnoea . excessive tearing . eye inflammation . fever . fluid imbalance . flushing . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headaches . insomnia . joint disorders . muscle complaints . nausea . neutropenia . oedema . pain . photosensitivity reaction . sensation abnormal . skin reactions . sweat changes . taste altered . thrombocytopenia . vision blurred . vomiting . weight changes

▶ Uncommon Anxiety . arrhythmias . ascites . breast abnormalities . broken nails . burping . chest pain . CNS haemorrhage . congestive heart failure . depression . drowsiness . dysphagia . electrolyte imbalance . eosinophilia . eye discomfort . gout . gynaecomastia . hearing loss . hepatic disorders . hyperbilirubinaemia . hyperglycaemia . hypertension . hyperuricaemia . hypotension . increased risk of infection . laryngeal pain . lymphadenopathy . lymphopenia . malaise . memory loss . menstrual cycle irregularities . nerve disorders . oral disorders . palpitations . pancreatitis . peripheral coldness . pulmonary oedema . Raynaud's phenomenon . renal impairment . renal pain . respiratory disorders . restless legs . scrotal oedema . sepsis . sexual dysfunction . syncope . thrombocytosis . tinnitus . tremor . urinary frequency increased . vertigo

▶ Rare or very rare Angina pectoris . angioedema . arthritis .

cardiac arrest . cataract . confusion . glaucoma . haemolytic anaemia . haemorrhagic ovarian cyst . hepatic failure (including fatal cases) . hypersensitivity vasculitis . inflammatory bowel disease . intracranial pressure increased . muscle weakness . myocardial infarction . myopathy . nail discolouration . pericardial disorders . pulmonary hypertension . seizure . severe cutaneous adverse reactions (SCARs) . thrombotic microangiopathy . tumour lysis syndrome

▶ Frequency not known Embolism and thrombosis . hepatitis B reactivation . neoplasm complications . osteonecrosis . pericarditis

ı CONCEPTION AND CONTRACEPTION Effective contraception required during treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı HEPATIC IMPAIRMENT Manufacturer advises caution.

Dose adjustments Manufacturer advises max. 400mg once daily; consider further dose reduction if not tolerated—consult product literature.

ı RENAL IMPAIRMENT Manufacturer advises use with caution.

Dose adjustments Manufacturer advises maximum starting dose 400mg daily; reduce dose further if not tolerated (consult product literature).

ı MONITORING REQUIREMENTS

▶ Monitor for gastrointestinal haemorrhage.

▶ Monitor complete blood counts regularly.

▶ Monitor for fluid retention.

▶ Monitor liver function.

▶ Monitor growth in children (may cause growth retardation).

ı DIRECTIONS FOR ADMINISTRATION Manufacturer advises tablets may be dispersed in water or apple juice.

ı PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer imatinib tablets.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Imatinib for the adjuvant treatment of gastro-intestinal stromal tumours (November 2014) NICE TA326 Recommended

▶ Imatinib for chronic myeloid leukaemia (updated January 2016) NICE TA70 Recommended

▶ Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (updated November 2010) NICE TA86 Recommended with restrictions

▶ Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (November 2010) NICE TA209 Not recommended

▶ Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA426 Recommended

▶ Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425 Not recommended

Scottish Medicines Consortium (SMC) decisions

▶ Imatinib (Glivec ●) for chronic myeloid leukaemia (January 2003) SMC No. 26/02 Recommended with restrictions

▶ Imatinib (Glivec ●) for the adjuvant treatment of gastrointestinal stromal tumours (September 2010) SMC No. 584/09 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 27

▶ Imatinib (Non-proprietary)

Imatinib (as Imatinib mesilate) 100 mg Imatinib 100mg tablets | 60 tabletP £973.32 DT = £333.41 | 60 tabletP £104.49 DT = £333.41 (Hospital only)

Imatinib (as Imatinib mesilate) 400 mg Imatinib 400mg tablets | 30 tabletP £1,946.67 DT = £641.83 | 30 tabletP £208.98 DT = £641.83 (Hospital only)

▶ Glivec (Novartis Pharmaceuticals UK Ltd) A

Imatinib (as Imatinib mesilate) 100 mg Glivec 100mg tablets | 60 tabletP £973.32 DT = £333.41

Imatinib (as Imatinib mesilate) 400 mg Glivec 400mg tablets | 30 tabletP £1,946.67 DT = £641.83

Lapatinib 10-Jun-2021

I DRUG ACTION Lapatinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Treatment of metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2) with hormone-receptornegative disease who have had previous treatment with trastuzumab in combination with chemotherapy (in combination with trastuzumab)

▶ BY MOUTH

▶ Adult: 1 g once daily

Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for patients who have had previous treatment with an anthracycline, a taxane, and trastuzumab (in combination with capecitabine)

▶ BY MOUTH

▶ Adult: 1.25 g once daily

Treatment of metastatic breast cancer with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for postmenopausal women with hormonereceptor-positive disease (in combination with an aromatase inhibitor)

▶ BY MOUTH

▶ Adult: 1.5 g once daily

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CAUTIONS Diarrhoea—withhold treatment if severe (consult product literature) . low gastric pH (reduced absorption) . susceptibility to QT-interval prolongation (including electrolyte disturbances)

I INTERACTIONS → Appendix 1: lapatinib

I SIDE-EFFECTS

▶ Common or very common Alopecia . appetite decreased . arthralgia . asthenia . constipation . cough . dehydration . diarrhoea (treat promptly) . dyspnoea . epistaxis . gastrointestinal discomfort . headache . hepatotoxicity (discontinue permanently if severe) . hot flush . hyperbilirubinaemia . insomnia . mucositis . nail disorder . nausea . pain . paronychia . skin reactions . stomatitis . vomiting

▶ Uncommon Respiratory disorders

▶ Frequency not known Severe cutaneous adverse reactions (SCARs)

I CONCEPTION AND CONTRACEPTION Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Discontinue breast-feeding.

I HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment—increased exposure (limited information available).

I RENAL IMPAIRMENT gCaution in severe impairment (no information available). M

I MONITORING REQUIREMENTS

▶ Monitor left ventricular function.

▶ Monitor for pulmonary toxicity.

▶ Monitor liver function before treatment and at monthly intervals.

I DIRECTIONS FOR ADMINISTRATION Manufacturer advises always take at the same time in relation to food: either one hour before or one hour after food.

I PATIENT AND CARER ADVICE Counselling advised (administration). Patients should be advised to report any unexpected changes in bowel habit.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormonereceptor-positive breast cancer that overexpresses HER2 (June 2012) NICE TA257 Not recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Tyverb (Novartis Pharmaceuticals UK Ltd)

Lapatinib (as Lapatinib ditosylate monohydrate) 250 mg Tyverb 250mg tablets | 84 tabletP £965.16 | 105 tabletP £1,206.45

Larotrectinib 03-Jun-2020

I DRUG ACTION Larotrectinib is a tropomyosin receptor kinase inhibitor.

I INDICATIONS AND DOSE

Solid tumours with neurotrophic tyrosine receptor kinase gene fusion (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 100 mg twice daily, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce dose by 50%.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I INTERACTIONS → Appendix 1: larotrectinib

I SIDE-EFFECTS

▶ Common or very common Anaemia . constipation . dizziness . fatigue . gait abnormal . leucopenia . muscle weakness . myalgia . nausea . neutropenia . paraesthesia . taste altered . vomiting . weight increased

I CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception in females of childbearing potential and in men with a partner of childbearing potential, during treatment and for 1 month after last treatment; additional barriermethod recommended in women using hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY Manufacturer advises avoid—limited information available. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid during treatment and for 3 days after last treatment—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (increased risk of exposure).

Dose adjustments Manufacturer advises dose reduction by 50% in moderate to severe impairment.

I MONITORING REQUIREMENTS Manufacturer advises monitor liver function (including ALT and AST) at baseline, then monthly during the first 3 months of treatment, and periodically thereafter; more frequent monitoring should be performed in patients who develop transaminase elevations. Treatment should be withheld or permanently discontinued based on severity—consult product literature.

I HANDLING AND STORAGE For oral solution, manufacturer advises store in a refrigerator (2–8°C).

I PATIENT AND CARER ADVICE

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness and fatigue.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Larotrectinib for treating NTRK fusion-positive solid tumours (May 2020) NICE TA630 Recommended with restrictions

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Oral solution

EXCIPIENTS: May contain Hydroxybenzoates (parabens), potassium sorbate, propylene glycol, sorbitol, sucrose

▶ Larotrectinib (non-proprietary) A

Larotrectinib (as Larotrectinib sulfate) 20 mg per 1 ml Vitrakvi 20mg/ml oral solution sugar free sugar-free | 100 mlP £5,000.00 (Hospital only)

▶ Vitrakvi (Bayer Plc) A

Larotrectinib (as Larotrectinib sulfate) 20 mg per 1 ml Vitrakvi 20mg/ml oral solution | 100 mlP £5,000.00 (Hospital only)

Capsule

CAUTIONARY AND ADVISORY LABELS 25

EXCIPIENTS: May contain Gelatin, propylene glycol

▶ Vitrakvi (Bayer Plc) A

Larotrectinib (as Larotrectinib sulfate) 25 mg Vitrakvi 25mg capsules | 56 capsuleP £3,500.00 (Hospital only)

Larotrectinib (as Larotrectinib sulfate) 100 mg Vitrakvi 100mg capsules | 56 capsule£ £14,000.00 (Hospital only)

Lenvatinib 10-Nov-2020

I DRUG ACTION Lenvatinib is a multireceptor tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

KISPLYX •

Advanced renal cell carcinoma following one prior vascular endothelial growth factor-targeted therapy (in combination with everolimus) (specialist use only)

▶ BY MOUTH

▶ Adult: 18 mg once daily, dose should be taken at the same time every day, for dose adjustment due to sideeffects—consult product literature

LENVIMA •

Differentiated thyroid carcinoma (specialist use only)

▶ BY MOUTH

▶ Adult: 24 mg once daily, dose should be taken at the same time every day, for dose adjustments due to sideeffects—consult product literature

Hepatocellular carcinoma (specialist use only)

▶ BY MOUTH

▶ Adult (body-weight up to 60 kg): 8 mg once daily, dose should be taken at the same time every day, for dose adjustments due to side-effects—consult product literature

▶ Adult (body-weight 60 kg and above): 12 mg once daily, dose should be taken at the same time every day, for dose adjustments due to side-effects—consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with lenvatinib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CONTRA-INDICATIONS Fistulae

I CAUTIONS Arterial thromboembolism within the previous 6 months . elderly (75 years and over)—reduced tolerability . hypertension . impaired wound healing—consider temporary interruption of treatment for major surgical procedures . risk factors for aneurysm or artery dissection

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

I INTERACTIONS → Appendix 1: lenvatinib

I SIDE-EFFECTS

▶ Common or very common Alopecia . appetite decreased . arthralgia . asthenia . cerebrovascular insufficiency . cholecystitis . constipation . decreased leucocytes . dehydration . diarrhoea . dizziness . dry mouth . dysphonia . electrolyte imbalance . embolism and thrombosis . encephalopathy . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . heart failure . hepatic coma . hepatic disorders . hyperbilirubinaemia . hypercholesterolaemia . hypertension . hypoalbuminaemia . hypotension . hypothyroidism . increased risk of infection . insomnia . malaise . mucositis . myalgia . myocardial infarction . nausea . neutropenia . oral disorders . oropharyngeal complaints . pain . peripheral oedema . proteinuria .QT interval prolongation . renal impairment . renal tubular necrosis . skin reactions . taste altered . thrombocytopenia . vomiting . weight decreased

▶ Uncommon Healing impaired . nephrotic syndrome . pancreatitis . paresis . pneumothorax . splenic infarction

▶ Frequency not known Aneurysm . artery dissection . cardiac disorder . cardiogenic shock . fistula

SIDE-EFFECTS, FURTHER INFORMATION Manufacturer advises gastrointestinal toxicity should be actively managed— dehydration and/or hypovolaemia caused by gastrointestinal toxicity are identified as primary risk factors for renal impairment or failure.

CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use highly effective contraception during treatment and for 1 month after the last dose, an additional barrier method of contraception should be used in women using oral hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—teratogenic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT

KISPLYX • Manufacturer advises caution in severe impairment (risk of increased exposure).

Dose adjustments Manufacturer advises dose reduction to 10 mg once daily in severe impairment.

LENVIMA • Manufacturer advises caution.

▶ When used for Hepatocellular carcinoma Manufacturer advises avoid in severe impairment (no information available).

Dose adjustments

▶ When used for Differentiated thyroid carcinoma Manufacturer advises dose reduction to 14mg once daily in severe impairment; further dose adjustments may be necessary based on tolerability—consult product literature.

RENAL IMPAIRMENT

KISPLYX • Manufacturer advises avoid in end-stage renal disease.

Dose adjustments Manufacturer advises reduce dose to 10 mg once daily in severe impairment; further dose adjustments may be necessary based on individual tolerability—consult product literature.

LENVIMA •

▶ When used for Differentiated thyroid carcinoma Manufacturer advises caution in severe impairment; avoid in end-stage renal disease.

▶ When used for Hepatocellular carcinoma The available data do not allow for a dosing recommendation in severe impairment—consult product literature.

Dose adjustments

▶ When used for Differentiated thyroid carcinoma Manufacturer advises dose reduction to 14mg once daily in severe impairment; further dose adjustments may be necessary based on tolerability—consult product literature.

MONITORING REQUIREMENTS

▶ Manufacturer advises monitor for signs and symptoms of cardiac decompensation (adjust dose as necessary—consult product literature).

▶ Manufacturer advises monitor liver function before treatment, then every 2 weeks for the first 2 months, and then monthly thereafter; monitor urine protein regularly.

▶ Manufacturer advises monitor ECG and electrolytes before and periodically during treatment (calcium levels should be monitored at least monthly), correct electrolyte abnormalities prior to treatment; monitor thyroid function before and regularly during treatment.

DIRECTIONS FOR ADMINISTRATION Manufacturer advises capsules should be swallowed whole. Alternatively, capsules may be added to a tablespoon of water or apple juice in a small glass (without breaking or crushing), allowed to sit for at least 10 minutes, then stirred for at least 3 minutes to dissolve the capsule shells before swallowing; the same amount of liquid should then be added to the glass, swirled a few times, then swallowed.

PATIENT AND CARER ADVICE

Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue and dizziness.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (August 2018) NICE TA535 Recommended with restrictions
▶ Lenvatinib for untreated advanced hepatocellular carcinoma (December 2018) NICE TA551 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Lenvatinib (Lenvima ∗) as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (April 2019) SMC No. SMC2138 Recommended
▶ Lenvatinib (Kisplyx ∗) in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy (November 2019) SMC No. SMC2199 Recommended
KISPLYX ∗ For full details see funding body website
NICE decisions
▶ Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (January 2018) NICE TA498 Recommended with restrictions
LENVIMA ∗ For full details see funding body website
Scottish Medicines Consortium (SMC) decisions
▶ Lenvatinib (Lenvima ∗) for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) (October 2016) SMC No. 1179/16 Recommended
ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Capsule
CAUTIONARY AND ADVISORY LABELS 25
▶ Kisplyx (Eisai Ltd)
Lenvatinib (as Lenvatinib mesilate) 4 mg Kisplyx 4mg capsules | 30 capsulesP £1,437.00 (Hospital only)
Lenvatinib (as Lenvatinib mesilate) 10 mg Kisplyx 10mg capsules | 30 capsulesP £1,437.00 (Hospital only)
▶ Lenvima (Eisai Ltd)
Lenvatinib (as Lenvatinib mesilate) 4 mg Lenvima 4mg capsules | 30 capsulesP £1,437.00 (Hospital only)
Lenvatinib (as Lenvatinib mesilate) 10 mg Lenvima 10mg capsules | 30 capsulesP £1,437.00 (Hospital only)

Lorlatinib 01-Apr-2022

ı DRUG ACTION Lorlatinib is a tyrosine kinase inhibitor.
ı INDICATIONS AND DOSE
Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (specialist use only)
▶ BY MOUTH
▶ Adult: 100 mg daily, for dose adjustments due to sideeffects—consult product literature
DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce starting dose to 75 mg once daily.
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
ı CAUTIONS Cardiac risk factors or conditions which may affect left ventricular ejection fraction—consider cardiac monitoring, including assessment of left ventricular ejection fraction, at baseline and during treatment . lactose intolerance . worsening respiratory symptoms indicative of interstitial lung disease or pneumonitis (including dyspnoea, cough, and fever)—withhold or permanently discontinue treatment based on severity
ı INTERACTIONS → Appendix 1: lorlatinib
ı SIDE-EFFECTS
▶ Common or very common Anaemia . anxiety . arthralgia . asthenia . behaviour abnormal . cognitive disorder .

concentration impaired . confusion . constipation . delirium . dementia . depression . diarrhoea . dyslipidaemia . gait abnormal . hallucinations . headache . inflammation . learning disability . memory loss . mental impairment (thought disturbance) . mood altered . muscle weakness . myalgia . nausea . nerve disorders . neurotoxicity . oedema . pain . peroneal nerve palsy . respiratory disorders . sensation abnormal . skin reactions . speech impairment . vision disorders . vitreous floater . weight increased

▶ Frequency not known Atrioventricular block

ı CONCEPTION AND CONTRACEPTION Manufacturer advises females of childbearing potential should use effective nonhormonal contraception during treatment and for 35 days after last treatment; male patients should use effective contraception during treatment and for 14 weeks after last treatment if their partner is pregnant or of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid during treatment and for 7 days after last treatment—no information available.

ı HEPATIC IMPAIRMENT Manufacturer advises avoid in moderate to severe impairment (no information available).

ı RENAL IMPAIRMENT Manufacturer advises avoid in severe impairment (limited information available).

ı MONITORING REQUIREMENTS

▶ Manufacturer advises monitor serum cholesterol and triglycerides before starting treatment, then at weeks 2, 4, and 8, and regularly thereafter.

▶ Manufacturer advises monitor ECG before starting treatment and monthly thereafter, particularly in patients with predisposing conditions.

▶ Manufacturer advises monitor for lipase and amylase elevations before starting treatment, and regularly thereafter as clinically indicated.

ı PATIENT AND CARER ADVICE

Missed doses Manufacturer advises if a dose is more than 20 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of CNS effects.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Lorlatinib for previously treated ALK-positive advanced nonsmall-cell lung cancer (May 2020) NICE TA628 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Lorlatinib (Lorviqua ⁎) as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy or crizotinib and at least one other ALK TKI (March 2020) SMC No. SMC2239 Recommended

▶ Lorlatinib (Lorviqua ⁎) as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously not treated with an ALK inhibitor (March 2022) SMC No. SMC2415 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25

▶ Lorviqua (Pfizer Ltd) A

Lorlatinib 25 mg Lorviqua 25mg tablets | 90 tabletP £5,283.00 (Hospital only) | 120 tabletP £7,044.00 (Hospital only)

Lorlatinib 100 mg Lorviqua 100mg tablets | 30 tabletP £5,283.00 (Hospital only)

Midostaurin 01-Oct-2021

ı DRUG ACTION Midostaurin is an inhibitor of multiple tyrosine kinases.

ı INDICATIONS AND DOSE

Acute myeloid leukaemia (specialist use only)

▶ BY MOUTH

▶ Adult: 50 mg twice daily, on days 8–21 of induction and consolidation chemotherapy cycles; for administration following consolidation chemotherapy, and dose adjustment or treatment interruption due to sideeffects—consult product literature

Aggressive systemic mastocytosis (specialist use only) | Systemic mastocytosis with associated haematological neoplasm (specialist use only) | Mast cell leukaemia (specialist use only)

▶ BY MOUTH

▶ Adult: 100 mg twice daily, for dose adjustment or treatment interruption due to side-effects—consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı CAUTIONS Active severe infection (control before

initiation of monotherapy) . elderly (limited experience) . patients at risk of congestive heart failure . risk factors for QT-interval prolongation

I INTERACTIONS → Appendix 1: midostaurin

I SIDE-EFFECTS

▶ Common or very common Asthenia . bruising . chills . concentration impaired . constipation . cough . cystitis . diarrhoea . dizziness . dyspepsia . dyspnoea . fall . febrile neutropenia . fever . haemorrhage . headache . hyperglycaemia . hypersensitivity . hypotension . increased risk of infection . nausea . oedema . oropharyngeal pain . QT interval prolongation . respiratory disorders . sepsis . tremor . vertigo . vomiting . weight increased

▶ Frequency not known Cardiac disorder . congestive heart failure

I CONCEPTION AND CONTRACEPTION Manufacturer advises perform pregnancy test in women of childbearing potential within 7 days prior to treatment initiation; effective contraception must be used during treatment and for at least 4 months after stopping treatment—additional barrier method recommended in women using hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Manufacturer advises avoid during treatment and for 4 months after stopping treatment—present in milk in animal studies.

I HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment and monitor for toxicity—no information available.

I RENAL IMPAIRMENT Manufacturer advises caution in severe impairment and monitor for toxicity—limited information available.

I MONITORING REQUIREMENTS

▶ Manufacturer advises monitor white blood cell count regularly, especially at treatment initiation; also monitor for signs and symptoms of infection.

▶ Manufacturer advises assess left ventricular ejection fraction in patients at risk of congestive heart failure at baseline and during treatment as clinically indicated; consider performing ECGs if concomitant use with drugs that can prolong QT-interval.

▶ Manufacturer advises monitor for pulmonary symptoms indicative of interstitial lung disease or pneumonitis.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Midostaurin for untreated acute myeloid leukaemia (June 2018) NICE TA523 Recommended with restrictions

▶ Midostaurin for treating advanced systemic mastocytosis (September 2021) NICE TA728 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Midostaurin (Rydapt ®) for treatment of adult patients with newly diagnosed acute myeloid leukaemia who are FLT3 mutation positive in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy (June 2018) SMC No. 1330/18 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

EXCIPIENTS: May contain Alcohol

▶ Rydapt (Novartis Pharmaceuticals UK Ltd) A

Midostaurin 25 mg Rydapt 25mg capsules | 56 capsuleP £5,609.94

Neratinib 11-Feb-2021

I DRUG ACTION Neratinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

HER2-overexpressed/amplified breast cancer (specialist use only)

▶ BY MOUTH

▶ Adult: 240 mg once daily for 1 year, dose to be taken with food, preferably in the morning, for dose adjustments due to side-effects—consult product

literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ If concurrent use of moderate CYP3A4 inhibitors or ciclosporin is unavoidable, reduce neratinib dose to 40mg once daily. If tolerated, increase dose by 40 mg at least every 7 days; max. dose 160mg daily.

▶ If concurrent use of potent CYP3A4 inhibitors is unavoidable, reduce neratinib dose to 40 mg once daily. M

CAUTIONS Cardiac risk factors or conditions which may affect left ventricular ejection fraction—consider cardiac monitoring, including assessment of left ventricular ejection fraction, as clinically indicated . elderly (increased risk of complications of diarrhoea) . gastro-intestinal disorder (significant, chronic) with diarrhoea as a major symptom—no clinical experience

INTERACTIONS → Appendix 1: neratinib

SIDE-EFFECTS

▶ Common or very common Appetite decreased . dehydration . diarrhoea . dry mouth . epistaxis . fatigue . gastrointestinal discomfort . increased risk of infection . mucositis . muscle spasms . nail discolouration . nail disorders . nausea . oral disorders . skin reactions . vomiting . weight decreased

▶ Uncommon Renal failure

SIDE-EFFECTS, FURTHER INFORMATION Diarrhoea may be severe and associated with dehydration. Diarrhoea is more likely to occur during initiation and may be recurrent. Manufacturer advises prophylactic treatment, with antidiarrhoeal agent.

CONCEPTION AND CONTRACEPTION Manufacturer advises females of childbearing potential should use highly effective contraception during treatment and for 1 month after last treatment; an additional barrier method of contraception should be used in females using hormonal contraceptives. Male patients should use effective contraception during treatment and for 3 months after last treatment if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment (risk of increased exposure).

RENAL IMPAIRMENT Manufacturer advises caution in mild to moderate impairment (increased risk of complications of dehydration from diarrhoea); avoid in severe impairment (no information available).

MONITORING REQUIREMENTS Manufacturer advises monitor liver function (including ALT, AST, and total bilirubin) at 1 week, then monthly for the first 3 months, and every 6 weeks thereafter, during treatment or as clinically indicated. Treatment should be withheld or permanently discontinued, based on severity, in those who develop hepatotoxicity—consult product literature.

PRESCRIBING AND DISPENSING INFORMATION Prophylactic treatment with an anti-diarrhoeal should be initiated with the first dose, and maintained during the first 1–2 months of treatment—consult product literature.

The manufacturer of Nerlynx ◆ has provided a Risk minimisation materials document for healthcare professionals.

PATIENT AND CARER ADVICE A patient alert card, patient treatment journal, and patient guide should be provided.

Missed doses Manufacturer advises if a dose is missed, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue, dizziness, dehydration, and syncope.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab (November 2019) NICE TA612 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Neratinib (Nerlynx ◆) for extended adjuvant treatment of

adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago (August 2020) SMC No. SMC2251 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

▶ Nerlynx (Pierre Fabre Ltd) A

Neratinib (as Neratinib maleate) 40 mg Nerlynx 40mg tablets | 180 tabletP £4,500.00 (Hospital only)

Nilotinib 22-Feb-2021

I DRUG ACTION Nilotinib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Newly diagnosed chronic phase Philadelphia chromosome-positive chronic myeloid leukaemia (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 300 mg twice daily, for dose adjustments due to side-effects—consult product literature

Chronic and accelerated phase Philadelphia chromosomepositive chronic myeloid leukaemia resistant or intolerant to previous therapy, including imatinib (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 400 mg twice daily, for dose adjustments due to side-effects—consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE (MAY 2016): RISK OF HEPATITIS B VIRUS REACTIVATION WITH TYROSINE KINASE INHIBITORS

An EU wide review has concluded that nilotinib can cause hepatitis B virus reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.

I CAUTIONS Clinically significant bradycardia . congestive heart failure . hepatitis B infection . history of pancreatitis . recent myocardial infarction . susceptibility to QT-interval prolongation (including electrolyte disturbances) . unstable angina

CAUTIONS, FURTHER INFORMATION

▶ Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

I INTERACTIONS → Appendix 1: nilotinib

I SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . angina pectoris . anxiety . appetite abnormal . arrhythmias . arthralgia . asthenia . bone marrow disorders . cardiac conduction disorders . chest discomfort . constipation . cough . decreased leucocytes . depression . diabetes mellitus . diarrhoea . dizziness . dry eye . dyslipidaemia . dyspnoea . electrolyte imbalance . eosinophilia . eye discomfort . eye disorders . eye inflammation . fever . flushing . gastrointestinal discomfort . gastrointestinal disorders . headaches . hepatic disorders . hyperbilirubinaemia . hyperglycaemia . hypertension . increased risk of infection . insomnia . muscle complaints . muscle weakness . myocardial infarction . nausea . neoplasms . neutropenia . oedema . pain . palpitations . peripheral neuropathy .QT interval prolongation . respiratory disorders . sensation abnormal . skin reactions . sweat changes . taste altered . thrombocytopenia . vertigo . vomiting . weight changes

▶ Uncommon Atherosclerosis . cerebrovascular insufficiency . chills . cyanosis . erectile dysfunction . gout . haemorrhage . heart failure . hyperaemia . malaise . oral disorders . pancreatitis . peripheral vascular disease .

temperature sensation altered . vision disorders

▶ Frequency not known Breast abnormalities . chorioretinopathy . diastolic dysfunction . dry mouth . facial swelling . gynaecomastia . hepatitis B reactivation . hyperparathyroidism . hyperuricaemia . hypoglycaemia . lethargy . memory loss . menorrhagia . oesophageal pain . oropharyngeal pain . pericardial effusion . pericarditis . restless legs . sebaceous hyperplasia . syncope . tremor . urinary disorders . urine discolouration

ı CONCEPTION AND CONTRACEPTION Manufacturer advises highly effective contraception in women of childbearing potential during treatment and for up to two weeks after stopping treatment. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; see also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

ı HEPATIC IMPAIRMENT Manufacturer advises caution (risk of increased exposure).

ı MONITORING REQUIREMENTS

▶ Manufacturer advises monitor lipid profiles before initiating treatment, at 3 and 6 months, and then yearly thereafter; monitor blood glucose before initiating treatment and then periodically during treatment, as clinically indicated.

▶ Manufacturer advises monitor full blood count every 2 weeks for the first 2 months of treatment, then monthly thereafter, or as clinically indicated.

▶ Manufacturer advises perform baseline ECG before treatment and as clinically indicated thereafter; correct any electrolyte disturbances before treatment and monitor periodically during treatment.

▶ Manufacturer advises monitor and actively manage cardiovascular risk factors during treatment.

ı DIRECTIONS FOR ADMINISTRATION gFood should not be consumed 2 hours before and for at least one hour after each dose. Capsules should either be swallowed whole or the contents of each capsule may be dispersed in one teaspoon of apple sauce and taken immediately. M

ı PRESCRIBING AND DISPENSING INFORMATION All prescribers should be familiar with the Summary of Key Safety Recommendations for Tasigna ⚬ (nilotinib) provided by the manufacturer.

ı PATIENT AND CARER ADVICE Manufacturer advises patients and carers should seek immediate medical attention if signs or symptoms of cardiovascular events occur.

All patients should be provided with the Important Information About How to Take Your Medication leaflet provided by the manufacturer.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (CML) (December 2016) NICE TA426 Recommended with restrictions

▶ Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (CML) (December 2016) NICE TA425 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25, 27

▶ Tasigna (Novartis Pharmaceuticals UK Ltd)

Nilotinib (as Nilotinib hydrochloride monohydrate) 50 mg Tasigna 50mg capsules | 120 capsuleP £2,432.85 DT = £2,432.85

Nilotinib (as Nilotinib hydrochloride monohydrate) 150 mg Tasigna 150mg capsules | 112 capsuleP £2,432.85 DT = £2,432.85

Nilotinib (as Nilotinib hydrochloride monohydrate) 200 mg Tasigna 200mg capsules | 112 capsuleP £2,432.85 DT = £2,432.85

Nintedanib 23-Nov-2021

ı DRUG ACTION Nintedanib is a tyrosine protein kinase inhibitor.

ı INDICATIONS AND DOSE

OFEV •

Idiopathic pulmonary fibrosis (initiated by a specialist) | Chronic fibrosing interstitial lung disease with a progressive phenotype (initiated by a specialist) | Systemic sclerosis-associated interstitial lung disease (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 150 mg twice daily, reduced if not tolerated to 100 mg twice daily, for dose adjustments due to sideeffects, consult product literature

VARGATEF •

Treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel) (initiated under specialist supervision)

▶ BY MOUTH

▶ Adult: 200 mg twice daily on days 2–21 of a standard 21 day docetaxel cycle, for treatment following discontinuation of docetaxel and for dose adjustments due to side-effects, consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with nintedanib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı CONTRA-INDICATIONS

OFEV • Severe pulmonary hypertension

ı CAUTIONS History or risk factors for QT prolongation . hypertension . impaired wound healing . increased risk of bleeding . patients at high risk of cardiovascular disease . previous abdominal surgery . recent history of hollow organ perforation . risk factors for aneurysm or artery dissection . theoretical increased risk of gastrointestinal perforation . theoretical increased risk of venous thromboembolism

OFEV • Mild to moderate pulmonary hypertension

ı INTERACTIONS → Appendix 1: nintedanib

ı SIDE-EFFECTS

▶ Common or very common Abdominal pain . abscess . alopecia . appetite decreased . dehydration . diarrhoea . drug-induced liver injury . electrolyte imbalance . haemorrhage . headache . hyperbilirubinaemia . hypertension . mucositis . nausea . neutropenia . peripheral neuropathy . sepsis . skin reactions . stomatitis . thrombocytopenia . venous thromboembolism . vomiting . weight decreased

▶ Uncommon Gastrointestinal disorders . myocardial infarction . pancreatitis . renal impairment

▶ Frequency not known Aneurysm . artery dissection

ı ALLERGY AND CROSS-SENSITIVITY gContra-indicated in patients with peanut or soya hypersensitivity. M

ı CONCEPTION AND CONTRACEPTION Manufacturer advises exclude pregnancy before treatment and ensure effective contraception (in addition to barrier method) during treatment and for at least 3 months after last dose.

ı PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in mild impairment (risk of increased exposure); avoid in moderate to severe impairment (limited information available).

OFEV • Dose adjustments Manufacturer advises dose reduction to 100mg twice daily in mild impairment.

ı RENAL IMPAIRMENT gCaution in severe impairment

(no information available). M

MONITORING REQUIREMENTS

▶ The MHRA advises to monitor blood pressure regularly.

▶ For Vargatef ∗, manufacturer advises monitor full blood count before each treatment cycle and regularly thereafter; monitor hepatic function before each treatment cycle during combination therapy and monthly during monotherapy; monitor renal function during treatment; monitor for thromboembolic events; monitor prothrombin time, INR and for bleeding if used concomitantly with anticoagulants; monitor for cerebral bleeding in patients with stable brain metastases.

▶ For Ofev ∗ manufacturer advises monitor hepatic function before treatment initiation and during the first month of treatment, then at regular intervals during the subsequent 2 months and as clinically indicated thereafter; monitor renal function during treatment.

PRESCRIBING AND DISPENSING INFORMATION

VARGATEF ∗ Not to be taken on the same day as docetaxel therapy.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (July 2015) NICE TA347 Recommended with restrictions

▶ Nintedanib for treating idiopathic pulmonary fibrosis (January 2016) NICE TA379 Recommended with restrictions

▶ Nintedanib for treating progressive fibrosing interstitial lung diseases (November 2021) NICE TA747 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Nintedanib (Ofev ∗) in adults for the treatment of idiopathic pulmonary fibrosis (IPF) (October 2015) SMC No. 1076/15 Recommended with restrictions

▶ Nintedanib (Ofev ∗) for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype in adults (June 2021) SMC No. SMC2331 Recommended

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

EXCIPIENTS: May contain Lecithin

▶ Ofev (Boehringer Ingelheim Ltd)

Nintedanib (as Nintedanib esilate) 100 mg Ofev 100mg capsules | 60 capsuleP £2,151.10 (Hospital only)

Nintedanib (as Nintedanib esilate) 150 mg Ofev 150mg capsules | 60 capsuleP £2,151.10 (Hospital only)

▶ Vargatef (Boehringer Ingelheim Ltd)

Nintedanib (as Nintedanib esilate) 100 mg Vargatef 100mg capsules | 120 capsuleP £2,151.10 (Hospital only)

Nintedanib (as Nintedanib esilate) 150 mg Vargatef 150mg capsules | 60 capsuleP £2,151.10 (Hospital only)

Osimertinib 04-Feb-2022

DRUG ACTION Osimertinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Non-small cell lung cancer (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 80 mg once daily, for dose adjustment, interruption, or treatment discontinuation due to sideeffects—consult product literature

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CONTRA-INDICATIONS Congenital long QT syndrome

CAUTIONS Elderly (more frequent dose adjustments may be required) . history of interstitial lung disease . radiation pneumonitis requiring steroid treatment . risk factors for QTc interval prolongation

INTERACTIONS → Appendix 1: osimertinib

SIDE-EFFECTS

▶ Common or very common Diarrhoea . eyelid pruritus . increased risk of infection . nail discolouration . nail disorders . respiratory disorders . skin reactions . stomatitis

▶ Uncommon Cutaneous vasculitis . eye disorders . eye inflammation .QT interval prolongation

▶ Rare or very rare Stevens-Johnson syndrome

▶ Frequency not known Decreased leucocytes . neutropenia . thrombocytopenia

ı CONCEPTION AND CONTRACEPTION Manufacturer advises use of effective, non-hormonal, contraception during and for 2 months after treatment in women, and 4 months after treatment in men.
ı PREGNANCY Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.
ı BREAST FEEDING Manufacturer advises avoid—may be present in milk based on animal studies.
ı HEPATIC IMPAIRMENT Manufacturer advises avoid in severe impairment (no information available).
ı RENAL IMPAIRMENT Manufacturer advises caution in severe and end-stage impairment—limited information available.
ı PRE-TREATMENT SCREENING gEvidence of epidermal growth factor receptor (EGFR) mutation positive status is required before osimertinib treatment is initiated, and should be determined by an experienced laboratory using a validated test method. M
ı MONITORING REQUIREMENTS Manufacturer advises monitor ECG and electrolytes periodically in patients with risk factors for QTc interval prolongation; dose adjustment is advised if QTc interval is more than 500 milliseconds on at least 2 separate ECGs—consult product literature.
ı DIRECTIONS FOR ADMINISTRATION Manufacturer advises tablet may be dispersed in 50mL of non-carbonated water, by stirring until dispersed and swallowed immediately (do not crush). The residue must then be re-dispersed in an additional half a glass of water and immediately swallowed. Manufacturer advises if administration via a nasogastric tube is required, the tablet may be dispersed in 15mL of non-carbonated water, by stirring until dispersed and the residue re-dispersed in an additional 15mL of water (do not crush). The total 30mL of liquid should then be administered as per the nasogastric tube manufacturer's instructions with appropriate water flushes; the solution should be administered within 30 minutes of adding the tablets to water.
ı PATIENT AND CARER ADVICE
Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.
ı NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer (October 2020) NICE TA653 Recommended with restrictions
▶ Osimertinib for untreated EGFR mutation-positive non-smallcell lung cancer (October 2020) NICE TA654 Recommended
▶ Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (January 2022) NICE TA761 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Osimertinib (Tagrisso *) for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) (February 2017) SMC No. 1214/17 Recommended with restrictions
▶ Osimertinib (Tagrisso *) for adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (November 2021) SMC No. SMC2383 Recommended with restrictions
▶ Osimertinib (Tagrisso *) as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations (January 2022) SMC No. SMC2382 Recommended
ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
▶ Tagrisso (AstraZeneca UK Ltd) A
Osimertinib (as Osimertinib mesylate) 40 mg Tagrisso 40mg tablets | 30 tabletP £5,770.00
Osimertinib (as Osimertinib mesylate) 80 mg Tagrisso 80mg tablets | 30 tabletP £5,770.00

Palbociclib 19-Jul-2021

ı DRUG ACTION Palbociclib is a highly selective inhibitor of cyclin-dependent kinases 4 and 6, which leads to disruption of cancer cell proliferation.
ı INDICATIONS AND DOSE
Locally advanced or metastatic breast cancer (initiated by a specialist)
▶ BY MOUTH

▶ Adult: 125 mg once daily for 21 consecutive days of repeated 28 day cycles, for dose adjustments due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce palbociclib dose to 75mg once daily. If the CYP3A4 inhibitor is stopped, increase the palbociclib dose (after 3–5 half

lives of the inhibitor) to the dose used before starting the CYP3A4 inhibitor.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE: CDK4/6 INHIBITORS (ABEMACICLIB, PALBOCICLIB, RIBOCICLIB): REPORTS OF INTERSTITIAL LUNG DISEASE AND PNEUMONITIS, INCLUDING SEVERE CASES (JUNE 2021)

Interstitial lung disease and pneumonitis, in some cases severe or fatal, have been reported in patients being treated with CDK4/6 inhibitors, such as palbociclib. Healthcare professionals are advised to ask patients taking palbociclib about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnoea. Patients should be advised to seek advice right away if these symptoms occur. Healthcare professionals should ensure patients have a copy of the Patient Information Leaflet (PIL) for palbociclib.

INTERACTIONS → Appendix 1: palbociclib

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . asthenia . diarrhoea . dry eye . epistaxis . excessive tearing . fever . infection . leucopenia . mucositis . nausea . neutropenia . oral disorders . oropharyngeal complaints . respiratory disorders . skin reactions . taste altered . thrombocytopenia . vision blurred . vomiting

SIDE-EFFECTS, FURTHER INFORMATION Side-effects are reported when used in combination with letrozole or fulvestrant.

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception in women of childbearing potential during treatment and for at least 3 weeks after completing treatment. Male patients should use effective contraception during treatment and for at least 14 weeks after completing treatment if their partner is of childbearing potential. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).

Dose adjustments Manufacturer advises dose reduction to 75 mg once daily in severe impairment.

RENAL IMPAIRMENT Manufacturer advises caution and monitor closely for signs of toxicity in moderate-to-severe impairment.

MONITORING REQUIREMENTS Manufacturer advises monitor full blood count prior to starting therapy, at the start of each cycle, on day 14 of the first 2 cycles and as clinically indicated.

PATIENT AND CARER ADVICE

Missed doses Manufacturer advises to take palbociclib at the same time each day; if a dose is missed, the missed dose should not be taken and the next dose should be taken at the usual time.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (December 2017) NICE TA495 Recommended with restrictions

▶ Palbociclib with fulvestrant for treating hormone receptorpositive, HER2-negative, advanced breast cancer (January 2020) NICE TA619 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Palbociclib (Ibrance ®) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2

(HER2)-negative locally advanced or metastatic breast cancer: in combination with an aromatase inhibitor; or in combination with fulvestrant in women who have received prior endocrine therapy (December 2017) SMC No. 1276/17 Recommended with restrictions

▶ Palbociclib (Ibrance ▪) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer -in combination with fulvestrant in women who have received prior endocrine therapy (July 2019) SMC No. SMC2149 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 25

▶ Ibrance (Pfizer Ltd)

Palbociclib 75 mg Ibrance 75mg tablets | 21 tabletP £2,950.00 (Hospital only) | 63 tabletP £8,850.00 (Hospital only)

Palbociclib 100 mg Ibrance 100mg tablets | 21 tabletP £2,950.00 (Hospital only) | 63 tabletP £8,850.00 (Hospital only)

Palbociclib 125 mg Ibrance 125mg tablets | 21 tabletP £2,950.00 (Hospital only) | 63 tabletP £8,850.00 (Hospital only)

Pazopanib 07-Jul-2021

ı DRUG ACTION Pazopanib is a tyrosine kinase inhibitor.

ı INDICATIONS AND DOSE

First-line treatment of advanced renal cell carcinoma | Treatment of advanced renal cell carcinoma in patients who have had previous treatment with cytokine therapy

▶ BY MOUTH

▶ Adult: 800 mg daily, adjust dose in steps of 200mg according to tolerability; maximum 800 mg per day

Treatment of selective subtypes of advanced soft-tissue sarcoma

▶ BY MOUTH

▶ Adult: (consult product literature)

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 400mg daily.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with pazopanib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı CAUTIONS Cardiac disease . hypertension . increased risk of gastro-intestinal fistulas . increased risk of gastrointestinal perforation . increased risk of haemorrhage .

increased risk of thrombotic microangiopathy—permanently discontinue if symptoms develop . ischaemic stroke . myocardial infarction . risk factors for aneurysm or artery dissection . risk of thrombotic events . susceptibility to QT-interval prolongation (including electrolyte disturbances) . transient ischaemic attack

CAUTIONS, FURTHER INFORMATION

▶ Elective surgery Discontinue treatment 7 days before elective surgery and restart only if adequate wound healing.

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

ı INTERACTIONS → Appendix 1: pazopanib

ı SIDE-EFFECTS

▶ Common or very common Alopecia . appetite decreased . arthralgia . asthenia . bradycardia . cancer pain . cardiac disorder . chest pain . chills . cough . dehydration . diarrhoea . dizziness . drowsiness . dry mouth . dysphonia .

dyspnoea . electrolyte imbalance . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . hair colour changes . headache . hepatic disorders . hiccups . hyperbilirubinaemia . hyperhidrosis . hypertension . hypoalbuminaemia . hypothyroidism . increased risk of infection . insomnia . left ventricular dysfunction . leucopenia . mucosal abnormalities . muscle complaints . musculoskeletal pain . nail disorder . nausea . neutropenia . oedema . oral disorders . peripheral neuropathy . proteinuria . respiratory disorders . sensation abnormal . skin reactions . taste altered . thrombocytopenia . vasodilation . venous thromboembolism . vision blurred . vomiting . weight decreased

▶ Uncommon Cerebrovascular insufficiency . eye disorders . haemolytic uraemic syndrome . menstrual cycle irregularities . myocardial infarction . myocardial ischaemia . oropharyngeal pain . pancreatitis . photosensitivity reaction . polycythaemia .QT interval prolongation . rhinorrhoea . skin ulcer . thrombotic microangiopathy

▶ Rare or very rare Posterior reversible encephalopathy syndrome (PRES)

▶ Frequency not known Aneurysm . artery dissection

ı CONCEPTION AND CONTRACEPTION Effective contraception advised during treatment.

ı PREGNANCY Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment. Dose adjustments Manufacturer advises dose reduction to 200mg daily in moderate impairment.

ı RENAL IMPAIRMENT gUse with caution if creatinine clearance less than 30 mL/minute (no information available); Msee p. 21.

ı MONITORING REQUIREMENTS

▶ Monitor liver function before treatment and at weeks 3, 5, 7, and 9, then at months 3 and 4, and periodically thereafter as clinically indicated—consult product literature if elevated liver enzymes observed.

▶ Monitor for signs or symptoms of congestive heart failure—monitor left ventricular ejection fraction in patients at risk of heart failure before and during treatment.

▶ Monitor for proteinuria.

▶ Monitor thyroid function.

▶ Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including headache, hypertension, seizure, lethargy, confusion, visual and neurological disturbances)—permanently discontinue treatment if symptoms occur.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Pazopanib for the first-line treatment of advanced renal cell carcinoma (updated August 2013) NICE TA215 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Pazopanib (Votrient ⁎) for the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease (March 2011) SMC No. 676/11 Recommended with restrictions

▶ Pazopanib (Votrient ⁎) for the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy (December 2012) SMC No. 820/12 Not recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 23, 25

▶ Votrient (Novartis Pharmaceuticals UK Ltd)

Pazopanib (as Pazopanib hydrochloride) 200 mg Votrient 200mg tablets | 30 tabletP £560.50

Pazopanib (as Pazopanib hydrochloride) 400 mg Votrient 400mg tablets | 30 tabletP £1,121.00

Pemigatinib 01-Mar-2022

DRUG ACTION Pemigatinib is a protein kinase inhibitor that inhibits fibroblast growth factor receptors (FGFR).

INDICATIONS AND DOSE

Cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement (initiated by a specialist)

▶ BY MOUTH

▶ Adult: 13.5 mg once daily for 14 consecutive days of repeated 21-day cycles, to be taken at the same time each day, for dose adjustments, treatment interruption, or discontinuation due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ gIf concomitant use with potent CYP3A4 inhibitors is unavoidable, reduce pemigatinib dose to 9mg once daily in those taking 13.5 mg once daily, or to 4.5mg once daily in patients already taking a reduced dose. M

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CAUTIONS Clinically significant eye disorders (such as retinal disorders—consult product literature)

INTERACTIONS → Appendix 1: pemigatinib

SIDE-EFFECTS

▶ Common or very common Alopecia . arthralgia . constipation . diarrhoea . dry eye . dry mouth . electrolyte imbalance . eye disorders . fatigue . hair growth abnormal . increased risk of infection . nail discolouration . nail disorders . nausea . punctate keratitis . skin reactions . stomatitis . taste altered . vision blurred

▶ Frequency not known Soft tissue calcification

CONCEPTION AND CONTRACEPTION gFemales of childbearing potential and male patients with a partner of childbearing potential should use effective contraception during and for 1 week after stopping treatment; additional barrier method recommended in women using hormonal contraceptives. M

PREGNANCY gAvoid unless essential—toxicity in animal studies. MSee also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING gAvoid during and for 1 week after stopping treatment—no information available. M

HEPATIC IMPAIRMENT gCaution in severe impairment.M

Dose adjustments gDose reduction in severe impairment—consult product literature. M

RENAL IMPAIRMENT gCaution in severe impairment.M

Dose adjustments gReduce dose in severe impairment—consult product literature. M

MONITORING REQUIREMENTS

▶gMonitor serum phosphate—consult product literature.

▶ Eye examination, including optical coherence tomography, should be performed before treatment, every 2 months for the first 6 months, then every 3 months thereafter, and urgently if visual symptoms occur.

▶ Consider using alternative markers of renal function if serum creatinine is persistently raised—consult product literature. M

PATIENT AND CARER ADVICE

Missed doses If a dose is more than 4 hours late or vomiting occurs after taking a dose, no additional dose should be taken and the next dose should be taken at the normal scheduled time.

Driving and skilled tasks Patients and carers should be counselled on the effects on driving and performance of skilled tasks—increased risk of fatigue and visual disturbances.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (August 2021) NICE TA722 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Pemigatinib (Pemazyre ⁎) as monotherapy for the treatment of adults with locally advanced or metastatic

cholangiocarcinoma with a fibroblast growth factor receptor 2 gene fusion or rearrangement that have progressed after at least one prior line of systemic therapy (February 2022)
SMC No. SMC2399 Recommended
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Pemazyre (Incyte Biosciences UK Ltd) A
Pemigatinib 4.5 mg Pemazyre 4.5mg tablets | 14 tabletP
£7,159.00 (Hospital only)
Pemigatinib 9 mg Pemazyre 9mg tablets | 14 tabletP
£7,159.00 (Hospital only)
Pemigatinib 13.5 mg Pemazyre 13.5mg tablets | 14 tabletP
£7,159.00 (Hospital only)

Ponatinib 19-Jul-2021

I INDICATIONS AND DOSE
Treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate | Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate
▶ BY MOUTH
▶ Adult: 45 mg once daily, for dose adjustments due to side-effects or dose reduction due to risk of vascular occlusive events, consult product literature
DOSE ADJUSTMENTS DUE TO INTERACTIONS
▶ Manufacturer advises consider a reduced initial dose of 30mg daily with concurrent use of potent inhibitors of CYP3A4.
IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS (MAY 2016)
An EU wide review has concluded that ponatinib can cause hepatitis B reactivation; the MHRA recommends establishing hepatitis B virus status in all patients before initiation of treatment.
MHRA/CHM ADVICE (UPDATED APRIL 2017): PONATINIB: RISK OF VASCULAR OCCLUSIVE EVENTS—UPDATED ADVICE ON POSSIBLE DOSE REDUCTION
The benefits and risks of ponatinib were reviewed by the European Medicines Agency's Committee onMedicinal Products for Human Use in 2014, which recommended that strengthened warnings should be added to the product information aimed at minimising the risk of blood clots and blockages in the arteries. Additional long-term follow-up data are now available that support new advice on dose modification to reduce this risk. The MHRA advises that although the recommended starting dose of ponatinib remains unchanged, prescribers should consider reducing the dose for patients with chronic phase chronic myeloid leukaemia (CP-CML) who have achieved a major cytogenetic response while on treatment. The following factors should be taken into account in the individual patient assessment:
. cardiovascular risk;
. side-effects of ponatinib therapy (including cardiovascular and other dose-related toxicity);
. time to cytogenetic response;
. BCR-ABL transcript levels.
The MHRA recommends close monitoring of response, if dose reduction is undertaken.
MHRA/CHM ADVICE: PONATINIB (ICLUSIG ®): REPORTS OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (OCTOBER 2018)
Post-marketing cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving ponatinib.
Treatment should be interrupted if PRES is confirmed and resumed only once the event is resolved and if the benefit of continued treatment outweighs the risk.
Patients should be advised to contact their healthcare professional immediately if they develop sudden-onset severe headache, confusion, seizures, or vision changes.
MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)
A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may

lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been

reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with ponatinib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CAUTIONS Alcohol abuse—increased risk of pancreatitis . current severe hypertriglyceridaemia—increased risk of pancreatitis . discontinue treatment if a complete haematologic response has not occurred within 3 months . hepatitis B infection . history of myocardial infarction—do not use unless potential benefit outweighs potential risk . history of pancreatitis . history of stroke—do not use unless potential benefit outweighs potential risk . hypertension . risk factors for aneurysm or artery dissection

CAUTIONS, FURTHER INFORMATION

▶ Cardiovascular status Assess cardiovascular status before treatment—manage cardiovascular risk factors before and during treatment.

▶ Hepatitis B infection The MHRA advises that patients who are carriers of hepatitis B virus should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment; expert advice should be sought for patients who test positive for hepatitis B virus and in those with active infection.

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

INTERACTIONS → Appendix 1: ponatinib

SIDE-EFFECTS

▶ Common or very common Acute coronary syndrome . alopecia . anaemia . appetite decreased . arrhythmias . arthralgia . asthenia . cerebrovascular insufficiency . chills . constipation . cough . diarrhoea . dizziness . dry eye . dry mouth . dysphonia . dyspnoea . electrolyte imbalance . embolism and thrombosis . erectile dysfunction . eye inflammation . febrile neutropenia . fever . fluid imbalance . gastrointestinal discomfort . gastrooesophageal reflux disease . haemorrhage . headaches . heart failure . hyperglycaemia . hypertension . hypertriglyceridaemia . hyperuricaemia . hypothyroidism . increased risk of infection . influenza like illness . insomnia . ischaemic heart disease . lethargy . mass . muscle complaints . nausea . oedema . pain . pancreatitis . pancytopenia . pericardial effusion . peripheral neuropathy . peripheral vascular disease . pleural effusion . pulmonary hypertension . sensation abnormal . sepsis . skin reactions . stomatitis . sweat changes . vasodilation . vision disorders . vomiting . weight decreased

▶ Uncommon Cardiac discomfort . cardiomyopathy ischaemic . coronary vasospasm . hepatic disorders . hepatic failure (including fatal cases) . intracranial haemorrhage . left ventricular dysfunction . posterior reversible encephalopathy syndrome (PRES) . renal artery stenosis . splenic infarction . tumour lysis syndrome

▶ Frequency not known Aneurysm . artery dissection

CONCEPTION AND CONTRACEPTION Ensure effective contraception during treatment in men and women; effectiveness of hormonal contraception unknown—alternative or additional methods of contraception should be used.

PREGNANCY Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises discontinue breastfeeding—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution.

RENAL IMPAIRMENT gUse with caution if creatinine clearance less than 50 mL/minute (no information

available), Msee p. 21.

I MONITORING REQUIREMENTS

▶ Manufacturer advises monitor serum lipase every 2 weeks for the first 2 months and periodically thereafter—withhold treatment if lipase elevated and abdominal symptoms occur.

▶ Manufacturer advises a full blood count every 2 weeks for the first 3 months and then monthly thereafter or as clinically indicated.

▶ Manufacturer advises monitor liver function periodically.

▶ Manufacturer advises monitor for vascular occlusion or thromboembolism—interrupt treatment immediately if this occurs.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (June 2017) NICE TA451 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 25

▶ Iclusig (Incyte Biosciences UK Ltd) A

Ponatinib (as Ponatinib hydrochloride) 15 mg Iclusig 15mg tablets | 30 tabletP £2,525.00

Ponatinib (as Ponatinib hydrochloride) 30 mg Iclusig 30mg tablets | 30 tabletP £5,050.00

Ponatinib (as Ponatinib hydrochloride) 45 mg Iclusig 45mg tablets | 30 tabletP £5,050.00

Regorafenib 22-Oct-2021

I DRUG ACTION Regorafenib is an inhibitor of several protein kinases.

I INDICATIONS AND DOSE

Metastatic colorectal cancer (specialist use only) | Unresectable or metastatic gastrointestinal stromal tumours (specialist use only) | Hepatocellular carcinoma (specialist use only)

▶ BY MOUTH

▶ Adult: 160 mg once daily for 21 consecutive days of repeated 28-day cycles, for dose adjustment due to side effects—consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with regorafenib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CAUTIONS Ensure measures to prevent hand-foot skin reaction . Gilbert's syndrome—risk of hyperbilirubinaemia . history of ischaemic heart disease—monitor for signs and symptoms of myocardial ischaemia and interrupt treatment if signs of ischaemia or infarction develop . hypertension . may impair wound healing—withhold treatment for major surgical procedures . predisposition to bleeding . risk factors for aneurysm or artery dissection

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

I INTERACTIONS → Appendix 1: regorafenib

I SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . asthenia . diarrhoea . dry mouth . dysphonia . electrolyte imbalance . fever . gastrooesophageal reflux disease . haemorrhage . headache . hyperbilirubinaemia . hypertension . hyperuricaemia . hypothyroidism .

increased risk of infection . leucopenia . mucositis . musculoskeletal stiffness . nausea . pain . proteinuria . skin reactions . stomatitis . taste altered . thrombocytopenia . tremor . vomiting . weight decreased

▶ Uncommon Gastrointestinal fistula (discontinue) . gastrointestinal perforation (including fatal cases, discontinue) . hepatic disorders . myocardial infarction . myocardial ischaemia . nail disorder

▶ Rare or very rare Neoplasms . posterior reversible encephalopathy syndrome (PRES) . severe cutaneous adverse reactions (SCARs)

▶ Frequency not known Aneurysm . artery dissection

I CONCEPTION AND CONTRACEPTION Women of childbearing potential and men must use effective contraception during treatment and up to 8 weeks after last dose.

I PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING Avoid—present in milk in animal studies.

I HEPATIC IMPAIRMENT Manufacturer advises caution in moderate impairment (limited information available); avoid in severe impairment (no information available).

I MONITORING REQUIREMENTS

▶ Monitor blood count and coagulation parameters and consider permanent discontinuation in event of severe bleeding.

▶ Monitor hepatic function before treatment, then at least every two weeks for the first 2 months, then at least monthly thereafter and as clinically indicated—consult product literature if changes in liver function observed.

▶ Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including seizure, headache, altered mental status, visual disturbances or cortical blindness, with or without hypertension)—discontinue treatment if symptoms occur.

▶ Monitor biochemical, electrolyte and metabolic parameters during treatment; ensure measures to prevent hand-foot skin reaction—consult product literature if signs or symptoms develop.

I DIRECTIONS FOR ADMINISTRATION Manufacturer advises tablets should be taken at the same time each day, swallowed whole with water after a light meal that contains less than 30% fat.

I PATIENT AND CARER ADVICE Counselling advised (administration).

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours (November 2017) NICE TA488 Recommended with restrictions

▶ Regorafenib for previously treated advanced hepatocellular carcinoma (January 2019) NICE TA555 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Regorafenib (Stivarga ®) as a monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (May 2018) SMC No. 1316/18 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

ELECTROLYTES: May contain Sodium

▶ Stivarga (Bayer Plc)

Regorafenib 40 mg Stivarga 40mg tablets | 84 tabletP £3,744.00 (Hospital only)

Ribociclib 19-Jul-2021

I DRUG ACTION Ribociclib is an inhibitor of cyclindependent kinases 4 and 6, which are involved in cancer cell proliferation; their inhibition results in prevention of cancer cell growth.

I INDICATIONS AND DOSE

Locally advanced or metastatic breast cancer (specialist use only)

▶ BY MOUTH

▶ Adult: 600 mg once daily for 21 consecutive days of repeated 28 day cycles, to be taken at approximately the same time each day, preferably in the morning, for dose adjustments due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, reduce dose to 400mg once daily; in those already taking 400mg once daily, reduce dose to 200mg once daily.

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

MHRA/CHM ADVICE: CDK4/6 INHIBITORS (ABEMACICLIB, PALBOCICLIB, RIBOCICLIB): REPORTS OF INTERSTITIAL LUNG DISEASE AND PNEUMONITIS, INCLUDING SEVERE CASES (JUNE 2021)

Interstitial lung disease and pneumonitis, in some cases severe or fatal, have been reported in patients being treated with CDK4/6 inhibitors, such as ribociclib. Healthcare professionals are advised to ask patients taking ribociclib about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnoea. Patients should be advised to seek advice right away if these symptoms occur. Healthcare professionals should ensure patients have a copy of the Patient Information Leaflet (PIL) for ribociclib.

CONTRA-INDICATIONS Pre-existing QTc prolongation . risk factors for QTc prolongation (including concomitant use of drugs known to prolong QTc interval)

INTERACTIONS → Appendix 1: ribociclib

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . asthenia . back pain . constipation . cough .

decreased leucocytes . diarrhoea . dizziness . dry eye . dry mouth . dyspnoea . electrolyte imbalance . excessive tearing . fever . gastrointestinal discomfort . headache . hepatic disorders . increased risk of infection . nausea . neutropenia . oropharyngeal pain . peripheral oedema .QT interval prolongation . sepsis . skin reactions . stomatitis . syncope . taste altered . thrombocytopenia . vertigo . vomiting

▶ Frequency not known Respiratory disorders . toxic epidermal necrolysis

ALLERGY AND CROSS-SENSITIVITY Contra-indicated in patients with hypersensitivity to peanut or soya products.

HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (risk of increased exposure).

Dose adjustments Manufacturer advises initial dose reduction to 400mg once daily in moderate to severe impairment.

RENAL IMPAIRMENT Manufacturer advises use with caution in severe renal impairment—limited information available.

MONITORING REQUIREMENTS

▶ Manufacturer advises to perform full blood counts and liver function tests before initiating treatment, every 2 weeks for the first 2 cycles, at the beginning of the subsequent 4 cycles, and then as clinically indicated thereafter.

▶ Manufacturer advises to assess ECG before initiating treatment (only initiate treatment in patients with QTcF values <450 milliseconds); ECG should be repeated at approx. day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

▶ Manufacturer advises to monitor serum electrolytes (including potassium, calcium, phosphorus and magnesium) before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated; any abnormality should be corrected before initiating treatment.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (December 2017) NICE TA496 Recommended

▶ Ribociclib with fulvestrant for treating hormone receptorpositive, HER2-negative advanced breast cancer after endocrine therapy (March 2021) NICE TA687 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Ribociclib (Kisqali ∗) for use in combination with an aromatase inhibitor, for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrinebased therapy (March 2018) SMC No. 1295/18 Recommended
▶ Ribociclib (Kisqali ∗) for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy (November 2019) SMC No. SMC2198 Recommended with restrictions
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 3, 25
▶ Kisqali (Novartis Pharmaceuticals UK Ltd) A
Ribociclib (as Ribociclib succinate) 200 mg Kisqali 200mg tablets | 21 tabletP £983.33 | 42 tabletP £1,966.67 | 63 tabletP £2,950.00

Ruxolitinib 22-Oct-2021

I DRUG ACTION Ruxolitinib is a selective inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2.
I INDICATIONS AND DOSE
Disease-related splenomegaly or symptoms [in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis] (specialist use only) | Polycythaemia vera [in patients resistant to, or intolerant of, hydroxyurea] (specialist use only)
▶ BY MOUTH
▶ Adult: (consult product literature or local protocols)
IMPORTANT SAFETY INFORMATION
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CAUTIONS Assess risk of developing infection before treatment—do not initiate until active serious infections are resolved
CAUTIONS, FURTHER INFORMATION
▶ Tuberculosis Patients should be evaluated for latent and active tuberculosis before starting treatment and monitored for signs and symptoms of tuberculosis during treatment.
I INTERACTIONS → Appendix 1: ruxolitinib
I SIDE-EFFECTS
▶ Common or very common Anaemia . bruising . constipation . dizziness . dyslipidaemia . flatulence . haemorrhage . headache . hypertension . increased risk of infection . intracranial haemorrhage . neutropenia . sepsis . thrombocytopenia . weight increased
I CONCEPTION AND CONTRACEPTION Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 962.
I PREGNANCY Avoid—toxicity in animal studies.
I BREAST FEEDING Avoid—present in milk in animal studies.
I HEPATIC IMPAIRMENT Manufacturer advises caution.
Dose adjustments Manufacturer advises initial dose reduction—consult product literature.
I RENAL IMPAIRMENT
Dose adjustments gReduce dose in severe impairment (consult product literature). M
I MONITORING REQUIREMENTS
▶ Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
▶ Monitor for infection during treatment.
▶ Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (March 2016) NICE TA386 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Ruxolitinib (Jakavi ∗) for the treatment of adult patients with polycythaemia vera (PV) who are resistant to or intolerant of hydroxyurea (HU) (December 2019) SMC No. SMC2213 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Jakavi (Novartis Pharmaceuticals UK Ltd)

Ruxolitinib (as Ruxolitinib phosphate) 5 mg Jakavi 5mg tablets | 56 tabletP £1,428.00 DT = £1,428.00

Ruxolitinib (as Ruxolitinib phosphate) 10 mg Jakavi 10mg tablets | 56 tabletP £2,856.00 DT = £2,856.00

Ruxolitinib (as Ruxolitinib phosphate) 15 mg Jakavi 15mg tablets | 56 tabletP £2,856.00 DT = £2,856.00

Ruxolitinib (as Ruxolitinib phosphate) 20 mg Jakavi 20mg tablets | 56 tabletP £2,856.00 DT = £2,856.00

Selpercatinib 26-Jan-2022

I DRUG ACTION Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.

I INDICATIONS AND DOSE

Non-small cell lung cancer [RET fusion-positive] (specialist use only) | Thyroid cancer [RET fusionpositive] (specialist use only) | Thyroid cancer [RETmutant] (specialist use only)

▶ BY MOUTH

▶ Adult (body-weight up to 50 kg): 120 mg twice daily, dose should be taken at the same time each day, for dose adjustments, treatment interruption, or discontinuation due to side-effects—consult product literature

▶ Adult (body-weight 50 kg and above): 160 mg twice daily, dose should be taken at the same time each day, for dose adjustments, treatment interruption, or discontinuation due to side-effects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ gReduce selpercatinib dose by 50% with concurrent use of potent CYP3A4 inhibitors and posaconazole. M

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CONTRA-INDICATIONS Uncontrolled hypertension

I CAUTIONS Susceptibility to QT-interval prolongation

I INTERACTIONS → Appendix 1: selpercatinib

I SIDE-EFFECTS

▶ Common or very common Abdominal pain . appetite decreased . arthralgia . constipation . diarrhoea . dizziness . dry mouth . fatigue . fever . haemorrhage . headache . hypersensitivity . hypertension . myalgia . nausea . oedema .QT interval prolongation . skin reactions . vomiting

▶ Frequency not known Intracranial haemorrhage . thrombocytopenia

I CONCEPTION AND CONTRACEPTION gFemales of childbearing potential and men with a partner of childbearing potential should use effective contraception during treatment and for one week after the last dose. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. MThe effect on human fertility is not known—impairment of fertility has been observed in animal studies.

I PREGNANCY gAvoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. M

I BREAST FEEDING gAvoid during treatment and for one week after the last dose (no information available). M

I HEPATIC IMPAIRMENT gCaution (risk of increased exposure). M

Dose adjustments gReduce dose to 80 mg twice daily in severe impairment. M

I MONITORING REQUIREMENTS

▶gMonitor liver transaminases before initiating treatment, then every 2 weeks during the first 3 months of treatment, then monthly thereafter and as clinically indicated.

▶ Monitor blood pressure before initiating and during treatment.

▶ Monitor ECG and serum electrolytes after 1 week of treatment, then monthly for the first 6 months of treatment, or as clinically indicated; more frequent monitoring may be required based on risk factors. M

I PATIENT AND CARER ADVICE gIf vomiting occurs after administration, no additional dose should be taken and the next dose should be taken at the normal time. M

Missed doses gIf a dose is missed, the missed dose should not be taken and the next dose should be taken at

the normal time. M
Driving and skilled tasks gPatients and their carers should be counselled on the effects on driving and skilled tasks—increased risk of fatigue and dizziness M
I NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Selpercatinib for treating advanced thyroid cancer with RET alterations (November 2021) NICE TA742 Recommended
▶ Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (January 2022) NICE TA760 Recommended
Scottish Medicines Consortium (SMC) decisions
▶ Selpercatinib (Retsevmo ®) as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib (September 2021) SMC No. SMC2370 Recommended
▶ Selpercatinib (Retsevmo ®) as monotherapy for the treatment of adults with advanced RET fusion-positive thyroid cancer (TC) who require systemic therapy following prior treatment with sorafenib and/or lenvatinib (September 2021) SMC No. SMC2370 Recommended
▶ Selpercatinib (Retsevmo ®) as monotherapy for the treatment of adults with advanced rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy (November 2021) SMC No. SMC2371 Not recommended
I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Capsule
CAUTIONARY AND ADVISORY LABELS 25
EXCIPIENTS: May contain Gelatin
▶ Retsevmo (Eli Lilly and Company Ltd) A
Selpercatinib 40 mg Retsevmo 40mg capsules | 56 capsuleP £2,184.00 (Hospital only) | 168 capsuleP £6,552.00 (Hospital only)
Selpercatinib 80 mg Retsevmo 80mg capsules | 56 capsuleP £4,368.00 (Hospital only) | 112 capsuleP £8,736.00 (Hospital only)

Sorafenib 13-Nov-2020

I DRUG ACTION Sorafenib is an inhibitor of multiple kinases.
I INDICATIONS AND DOSE
Treatment of advanced renal cell carcinoma when treatment with interferon alfa or interleukin-2 has failed or is unsuitable | Treatment of progressive, locally advanced, or metastatic, differentiated thyroid carcinoma that is refractory to radioactive iodine | Treatment of hepatocellular carcinoma
▶ BY MOUTH
▶ Adult: 400 mg twice daily, for dose adjustments due to side effects, consult product literature
IMPORTANT SAFETY INFORMATION
MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)
A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with sorafenib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES
See Cytotoxic drugs p. 962.
I CAUTIONS Cardiac ischaemia . hypertension . major surgical procedures . potential risk of bleeding—treat tracheal, bronchial, or oesophageal infiltration with localised therapy before initiating sorafenib in patients with differentiated thyroid carcinoma (DTC) and consider permanent withdrawal of sorafenib in any patient that requires medical intervention for bleeding . risk factors for aneurysm or artery dissection . susceptibility to QTinterval prolongation
CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

ı INTERACTIONS → Appendix 1: sorafenib

ı SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . appetite decreased . arthralgia . asthenia . congestive heart failure . constipation . decreased leucocytes . depression . diarrhoea . dry mouth . dysphagia . dysphonia . electrolyte imbalance . erectile dysfunction . fever . flushing . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . hypertension . hypothyroidism . increased risk of infection . influenza like illness . intracranial haemorrhage . mucositis . muscle complaints . myocardial infarction . myocardial ischaemia . nausea . neoplasms . neutropenia . oral disorders . pain . peripheral neuropathy . proteinuria . renal failure . rhinorrhoea . skin reactions . taste altered . thrombocytopenia . tinnitus . vomiting . weight decreased

▶ Uncommon Cholangitis . cholecystitis . dehydration . encephalopathy . gynaecomastia . hepatic disorders . hyperthyroidism . pancreatitis . radiation injuries . respiratory disorders

▶ Rare or very rare Angioedema . hypersensitivity vasculitis . nephrotic syndrome .QT interval prolongation . rhabdomyolysis . severe cutaneous adverse reactions (SCARs)

▶ Frequency not known Aneurysm . artery dissection

ı CONCEPTION AND CONTRACEPTION Contraceptive advice required, see Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı PREGNANCY Manufacturer advises avoid unless essential—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment (no information available).

ı MONITORING REQUIREMENTS

▶ Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation.

▶ Monitor plasma-calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroidism).

▶ Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009) NICE TA178 Not recommended

▶ Sorafenib for treating advanced hepatocellular carcinoma (September 2017) NICE TA474 Recommended with restrictions

▶ Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (August 2018) NICE TA535 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Sorafenib (Nexavar ⁎) for the treatment of hepatocellular carcinoma (January 2016) SMC No. 482/08 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 23

▶ Sorafenib (Non-proprietary)

Sorafenib (as Sorafenib tosylate) 200 mg Sorafenib 200mg tablets | 112 tabletP £2,567.00–£3,218.00 (Hospital only)

▶ Nexavar (Bayer Plc)

Sorafenib (as Sorafenib tosylate) 200 mg Nexavar 200mg tablets | 112 tabletP £3,576.56

Sunitinib 26-Nov-2020

ı DRUG ACTION Sunitinib is a tyrosine kinase inhibitor.

ı INDICATIONS AND DOSE

Treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib | Treatment of advanced or metastatic renal cell carcinoma

▶ BY MOUTH

▶ Adult: 50 mg once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle, adjusted in steps of 12.5 mg, doses adjusted according to tolerability; usual dose 25–75 mg daily

Treatment of unresectable or metastatic pancreatic neuroendocrine tumours

▶ BY MOUTH

▶ Adult: 37.5 mg once daily without treatment-free period; adjusted in steps of 12.5 mg, doses adjusted according to tolerability; maximum 50 mg per day

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ Manufacturer advises if concurrent use of potent inducers of CYP3A4 is unavoidable, dose may need to be increased in steps of 12.5mg to a max. dose of

87.5mg per day for gastro-intestinal stromal tumours or renal cell carcinoma, or to a max. dose of 62.5mg per day for pancreatic neuroendocrine tumours.

▶ Manufacturer advises if concurrent use of potent inhibitors of CYP3A4 is unavoidable, dose may need to be decreased to a minimum of 37.5mg per day for gastrointestinal stromal tumours or renal cell carcinoma, or to a minimum of 25 mg per day for pancreatic neuroendocrine tumours.

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: BEVACIZUMAB AND SUNITINIB: RISK OF OSTEONECROSIS OF THE JAW (JANUARY 2011)

Treatment with bevacizumab or sunitinib may be a risk factor for the development of osteonecrosis of the jaw. Patients treated with bevacizumab or sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk.

Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib.

If possible, invasive dental procedures should be avoided in patients treated with bevacizumab or sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with sunitinib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

ı CAUTIONS Cardiovascular disease—discontinue if congestive heart failure develops . hypertension . increased risk of bleeding . risk factors for aneurysm or artery dissection . susceptibility to QT-interval prolongation

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

ı INTERACTIONS → Appendix 1: sunitinib

ı SIDE-EFFECTS

▶ Common or very common Abscess . alopecia . anaemia . appetite decreased . arthralgia . burping . chest pain . chills . constipation . cough . dehydration . depression . diarrhoea . dizziness . dry mouth . dysphagia . dyspnoea . embolism and thrombosis . excessive tearing . eye inflammation . fatigue . fever . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . hair colour changes . headache . hypertension . hypoglycaemia . hypothyroidism . increased risk of infection . influenza like illness . insomnia . leucopenia . mucositis . muscle complaints . muscle weakness . myocardial ischaemia . nail

disorder . nasal complaints . nausea . neutropenia . oedema . oral disorders . oropharyngeal pain . pain . peripheral neuropathy . proteinuria . renal impairment . respiratory disorders . sensation abnormal . sepsis . skin reactions . taste altered . thrombocytopenia . urine discolouration . vasodilation . vomiting . weight decreased

▶ Uncommon Anal fistula (interrupt treatment) . cardiomyopathy . cerebrovascular insufficiency . cholecystitis . fistula (interrupt treatment) . healing impaired . heart failure . hepatic disorders . hypersensitivity . hyperthyroidism . intracranial haemorrhage . myocardial infarction . osteonecrosis of jaw . pancreatitis . pancytopenia . pericardial effusion .QT interval prolongation . tumour haemorrhage

▶ Rare or very rare Angioedema . myopathy . nephrotic syndrome . posterior reversible encephalopathy syndrome (PRES) . pyoderma gangrenosum . severe cutaneous adverse reactions (SCARs) . thrombotic microangiopathy . thyroiditis . torsade de pointes . tumour lysis syndrome

▶ Frequency not known Aneurysm . aortic dissection . artery dissection

ı CONCEPTION AND CONTRACEPTION Effective contraception required during treatment.

ı PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Discontinue breast-feeding.

ı MONITORING REQUIREMENTS Monitor for thyroid dysfunction.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (March 2009) NICE TA169 Recommended

▶ Sunitinib for the treatment of gastrointestinal stromal tumours (September 2009) NICE TA179 Recommended with restrictions

▶ Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009) NICE TA178 Not recommended

▶ Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (June 2017) NICE TA449 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Sunitinib (Sutent ⁎) for unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance (November 2009) SMC No. 275/06 Recommended

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 14

▶ Sunitinib (Non-proprietary)

Sunitinib (as Sunitinib malate) 12.5 mg Sunitinib 12.5mg capsules | 28 capsuleP £627.76–£784.70 (Hospital only) | 28 capsuleP £706.23

Sunitinib (as Sunitinib malate) 25 mg Sunitinib 25mg capsules | 28 capsuleP £1,224.13–£1,569.40 (Hospital only) | 28 capsuleP £1,412.46

Sunitinib (as Sunitinib malate) 50 mg Sunitinib 50mg capsules | 28 capsuleP £2,511.04–£3,138.80 (Hospital only)

▶ Sutent (Pfizer Ltd)

Sunitinib (as Sunitinib malate) 12.5 mg Sutent 12.5mg capsules | 28 capsuleP £784.70 (Hospital only)

Sunitinib (as Sunitinib malate) 25 mg Sutent 25mg capsules | 28 capsuleP £1,569.40 (Hospital only)

Sunitinib (as Sunitinib malate) 50 mg Sutent 50mg capsules | 28 capsuleP £3,138.80 (Hospital only)

Temsirolimus 11-Jun-2021

ı DRUG ACTION Temsirolimus is a protein kinase inhibitor.

ı INDICATIONS AND DOSE

First-line treatment of advanced renal cell carcinoma |

Treatment of relapsed or refractory mantle cell lymphoma

▶ BY INTRAVENOUS INFUSION

▶ Adult: (consult product literature or local protocols)

INTERACTIONS → Appendix 1: temsirolimus

SIDE-EFFECTS

▶ Common or very common Abscess . anaemia . anxiety . appetite decreased . arthralgia . asthenia . chest pain . chills . conjunctivitis . constipation . cough . cystitis . decreased leucocytes . dehydration . depression . diabetes mellitus . diarrhoea . dizziness . drowsiness . dyslipidaemia . dysphagia . dyspnoea . electrolyte imbalance . embolism and thrombosis . fever . gastrointestinal discomfort . gastrointestinal disorders . genital oedema . haemorrhage . headache . hypersensitivity . hypertension . increased risk of infection . insomnia . lacrimation disorder . mucositis . myalgia . nail disorder . nausea . neutropenia . oedema . oral disorders . pain . paraesthesia . post procedural infection . renal failure . respiratory disorders . scrotal oedema . sepsis . skin reactions . taste altered . thrombocytopenia . vomiting

▶ Uncommon Healing impaired . intracranial haemorrhage . pericardial effusion

SIDE-EFFECTS, FURTHER INFORMATION Hypersensitivity reactions, including some life-threatening and rare fatal reactions, are associated with temsirolimus therapy. Symptoms include flushing, chest pain, dyspnoea, apnoea, hypotension, loss of consciousness, and anaphylaxis. Patients should receive an intravenous dose of antihistamine 30 minutes before starting the temsirolimus infusion. The infusion may have to be stopped temporarily for the treatment of infusion-related effects—consult product literature for appropriate management. If adverse reactions are not managed with dose delays, a dose reduction should be considered—consult product literature.

CONCEPTION AND CONTRACEPTION Ensure effective contraception during treatment in men and women.

PREGNANCY Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises discontinue breast-feeding.

HEPATIC IMPAIRMENT

▶ When used for Renal cell carcinoma Manufacturer advises caution.

▶ When used for Mantle cell lymphoma Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

Dose adjustments

▶ When used for Renal cell carcinoma Manufacturer advises dose reduction in severe impairment—consult product literature.

RENAL IMPAIRMENT gCaution in severe impairment (no information available). M

MONITORING REQUIREMENTS

▶ Monitor respiratory function.

▶ Monitor blood lipids.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (August 2009) NICE TA178 Not recommended

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

EXCIPIENTS: May contain Ethanol, propylene glycol

▶ Torisel (Pfizer Ltd)

Temsirolimus 25 mg per 1 ml Torisel 30mg/1.2ml concentrate for solution for infusion vials and diluent | 1 vialP £620.00 (Hospital only)

Tepotinib 30-Nov-2021

DRUG ACTION Tepotinib is a kinase inhibitor which targets mesenchymal-epithelial transition (MET) factor gene including variants with exon 14 skipping alterations, thereby inhibiting tumour cell proliferation.

INDICATIONS AND DOSE

Non-small cell lung cancer with mesenchymal-epithelial transition factor gene (MET) exon 14 skipping

alterations (specialist use only)

▶ BY MOUTH

▶ Adult: 450 mg once daily, for dose adjustment, interruption, or treatment discontinuation due to sideeffects—consult product literature, discontinue treatment if patient unable to tolerate at least 225mg once daily

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I INTERACTIONS → Appendix 1: tepotinib

I SIDE-EFFECTS

▶ Common or very common Asthenia . constipation . diarrhoea . gastrointestinal discomfort . hepatic disorders . hypoalbuminaemia . nausea . oedema . respiratory disorders . vomiting

▶ Frequency not known Dyspnoea . musculoskeletal pain . pneumonia . pulmonary embolism

I CONCEPTION AND CONTRACEPTION gFemales of childbearing potential and male patients with female partners of childbearing potential should use effective contraception during treatment and for at least 1 week after last treatment. M

I PREGNANCY gAvoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962. M

I BREAST FEEDING gDiscontinue breast-feeding during treatment and for at least 1 week after last treatment—no information available. M

I HEPATIC IMPAIRMENT gCaution in severe impairment (no information available). M

I RENAL IMPAIRMENT gCaution in severe impairment (no information available).

Tepotinib may inhibit renal tubular transporter proteins leading to an increase in creatinine levels that is due to inhibition of active tubular secretion rather than renal injury. Caution is required when interpreting creatinine clearance or estimated glomerular filtration rate and further assessment of renal function is required—consult product literature. M

I MONITORING REQUIREMENTS

▶gMonitor liver enzymes and bilirubin before treatment initiation, then every 2 weeks for first three months and then once a month thereafter.

▶ Monitor for new or worsening pulmonary symptoms of dyspnoea, cough and fever which may develop during

treatment—increased risk of interstitial lung disease-like reactions. M

I PATIENT AND CARER ADVICE

Missed doses If a dose is more than 16 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Patients and carers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of fatigue or asthenia.

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

▶ Tepmetko (Merck Serono Ltd) A

Tepotinib (as Tepotinib hydrochloride) 225 mg Tepmetko 225mg tablets | 60 tabletP £7,200.00 (Hospital only)

Tivozanib 11-Nov-2020

I DRUG ACTION Tivozanib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Advanced renal cell carcinoma (specialist use only)

▶ BY MOUTH

▶ Adult: 1340 micrograms once daily for 21 consecutive days of repeated 28 day cycles, for dose adjustments due to side effects—consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare

professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with tivozanib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CAUTIONS History of arterial thromboembolic events . history of bleeding disorders . history of posterior reversible encephalopathy syndrome following tivozanib treatment . history of QT-interval prolongation . history of venous thromboembolic events . hypertension . major surgical procedures—interrupt treatment . patients aged over 65 years—increased risk of adverse effects . preexisting cardiac disease . risk factors for aneurysm or artery dissection . risk factors for arterial thromboembolic events . risk factors for gastro-intestinal fistula . risk factors for gastro-intestinal perforation . risk factors for venous thromboembolic events . risk of bleeding

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

INTERACTIONS → Appendix 1: tivozanib

SIDE-EFFECTS

▶ Common or very common Alopecia . anaemia . angina pectoris . appetite decreased . arrhythmias . arthralgia . asthenia . cancer pain . cerebrovascular insufficiency . chest pain . chills . constipation . cough . diarrhoea . dizziness . dry mouth . dysphonia . dyspnoea . embolism and thrombosis . fever . gastrointestinal discomfort . gastrointestinal disorders . haemorrhage . headache . hypertension . hypothermia . hypothyroidism . increased risk of infection . insomnia . ischaemia . myalgia . myocardial infarction . nasal complaints . nausea . nerve disorders . oral disorders . oropharyngeal pain . pain . pancreatitis . peripheral oedema . proteinuria . sensation abnormal . skin reactions . swallowing difficulty . taste altered . tinnitus . vasodilation . vertigo . vision disorders . vomiting . weight decreased

▶ Uncommon Coronary artery insufficiency . ear congestion . excessive tearing . goitre . hyperhidrosis . hyperthyroidism . memory loss . mucositis . muscle weakness . pulmonary oedema .QT interval prolongation . thrombocytopenia . toxic nodular goitre

▶ Rare or very rare Posterior reversible encephalopathy syndrome (PRES)

▶ Frequency not known Aneurysm . artery dissection . heart failure

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception in men, women of childbearing potential, and their partners during treatment and for at least one month after the last dose; an additional barrier method of contraception should be used in women using hormonal contraceptives. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution in mild-to-moderate impairment—monitor patients for tolerability; avoid in severe impairment.

Dose adjustments Manufacturer advises reduce dose to 1340 micrograms on alternate days in moderate impairment—increased risk of adverse effects due to increased exposure.

RENAL IMPAIRMENT Manufacturer advises caution in severe impairment—limited information available.

MONITORING REQUIREMENTS

▶ Manufacturer advises perform liver function tests (including ALT, AST and AP) before and during treatment; monitor for proteinuria before treatment and periodically thereafter.

▶ Manufacturer advises monitor for signs or symptoms of cardiac failure during treatment.
▶ Manufacturer advises perform baseline ECG and monitor electrolytes before treatment and as clinically indicated thereafter.
▶ Manufacturer advises monitor thyroid function before treatment and periodically thereafter.
▶ Manufacturer advises monitor for symptoms of gastrointestinal perforation or fistula.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Tivozanib for treating advanced renal cell carcinoma (March 2018) NICE TA512 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Tivozanib (Fotivda ®) for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are vascular endothelial growth factor receptor and mammalian target of rapamycin pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced RCC (July 2018) SMC No. 1335/18 Recommended with restrictions

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

▶ Fotivda (EUSA Pharma (UK) Ltd) A
Tivozanib (as Tivozanib hydrochloride monohydrate).89 mg Fotivda 890microgram capsules | 21 capsuleP £2,052.00 (Hospital only)
Tivozanib (as Tivozanib hydrochloride monohydrate) 1.34 mg Fotivda 1340microgram capsules | 21 capsuleP £2,052.00 (Hospital only)

Trametinib 30-Mar-2021

I DRUG ACTION Trametinib is a protein kinase inhibitor.

I INDICATIONS AND DOSE

Unresectable or metastatic melanoma with a BRAF V600 mutation (as monotherapy or in combination with dabrafenib) (specialist use only) | Advanced non-small cell lung cancer with a BRAF V600 mutation (in combination with dabrafenib) (specialist use only)

▶ BY MOUTH

▶ Adult: 2 mg once daily, when used in combination with dabrafenib, the dose should be taken at the same time each day with either the morning or evening dose of dabrafenib, for dose adjustments due to side-effects, consult product literature

Adjuvant treatment of stage III melanoma with a BRAF V600 mutation following complete resection (in combination with dabrafenib) (specialist use only)

▶ BY MOUTH

▶ Adult: 2 mg once daily for 12 months, the dose should be taken at the same time each day with either the morning or evening dose of dabrafenib, for dose adjustments due to side-effects, consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE (MARCH 2016): TRAMETINIB: RISK OF GASTROINTESTINAL PERFORATION AND COLITIS

A review by EU medicines regulators has concluded that trametinib can cause gastrointestinal perforation or colitis.

Trametinib should be used with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation. Prescribers should be vigilant for signs and symptoms of gastrointestinal perforation and should advise patients to seek urgent medical attention if they develop severe abdominal pain.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I CONTRA-INDICATIONS History of retinal vein occlusion

I CAUTIONS Concomitant antiplatelet or anticoagulant therapy—increased risk of haemorrhage . conditions that could impair left ventricular function . elderly (more frequent dose adjustments may be required) . impaired left ventricular function . predisposing factors for retinal vein occlusion . risk factors for gastrointestinal perforation

I INTERACTIONS → Appendix 1: trametinib

I SIDE-EFFECTS

▶ Common or very common Abdominal pain . alopecia . anaemia . asthenia . bradycardia . constipation . cough . dehydration . diarrhoea . dry mouth . dyspnoea . eye inflammation . fever . haemorrhage . hypersensitivity . hypertension . increased risk of infection . intracranial haemorrhage . left ventricular dysfunction . lymphoedema . mucositis . nausea . oedema . respiratory disorders . skin reactions . stomatitis . vision disorders . vomiting

▶ Uncommon Chorioretinopathy . gastrointestinal disorders . heart failure . retinal detachment . retinal occlusion . rhabdomyolysis

SIDE-EFFECTS, FURTHER INFORMATION Additional sideeffects reported when used in combination with dabrafenib include dizziness, hyperhidrosis, hyponatraemia, hypotension, leucopenia, muscle spasms, myocarditis, neutropenia, night sweats, and thrombocytopenia.

ı CONCEPTION AND CONTRACEPTION Manufacturer advises women of child-bearing potential should use highly effective non-hormonal contraception during, and for 4 months after stopping treatment.

ı PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Manufacturer advises avoid—no information available.

ı HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (no information available).

ı RENAL IMPAIRMENT Manufacturer advises caution in severe impairment—no information available.

ı MONITORING REQUIREMENTS Manufacturer advises measure blood pressure at baseline and monitor during treatment; evaluate left ventricular ejection fraction before treatment, after one month of treatment, and then approximately every 3 months thereafter; monitor liver function every 4 weeks for 6 months after treatment initiation, and thereafter as clinically indicated.

ı HANDLING AND STORAGE Manufacturer advises store in refrigerator (2–8 °C); once opened, bottle may be stored for 30 days at not more than 30 °C.

ı PATIENT AND CARER ADVICE Manufacturer advises patients and their carers should be told to seek immediate medical attention if symptoms of pulmonary embolism or deep vein thrombosis occur; patients and their carers should also be advised to report new visual disturbances.

Missed doses Manufacturer advises if a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Driving and skilled tasks Manufacturer advises patients and carers should be counselled on the effects on driving and performance of skilled tasks—risk of dizziness and visual disturbances.

ı NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (June 2016) NICE TA396 Recommended with restrictions

▶ Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (October 2018) NICE TA544 Recommended with restrictions

Scottish Medicines Consortium (SMC) decisions

▶ Trametinib (Mekinist ⁎) in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation [for firstline treatment] (September 2016) SMC No. 1161/16 Recommended with restrictions

▶ Trametinib (Mekinist ⁎) in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation [after firstline treatment] (March 2021) SMC No. SMC2328 Recommended with restrictions

ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 23, 25

▶ Mekinist (Novartis Pharmaceuticals UK Ltd)

Trametinib 500 microgram Mekinist 0.5mg tablets | 7 tabletP £280.00 | 30 tabletP £1,200.00

Trametinib 2 mg Mekinist 2mg tablets | 7 tabletP £1,120.00 |

30 tabletP £4,800.00

Tucatinib 04-May-2022

I DRUG ACTION Tucatinib is a tyrosine kinase inhibitor that inhibits human epidermal growth factor receptor-2 (HER2).

I INDICATIONS AND DOSE

HER2-positive breast cancer (specialist use only)

▶ BY MOUTH

▶ Adult: 300 mg twice daily, doses to be taken approximately 12 hours apart, for dose adjustments, treatment interruption, or discontinuation due to sideeffects—consult product literature

DOSE ADJUSTMENTS DUE TO INTERACTIONS

▶ gIf concurrent use with potent CYP2C8 inhibitors is unavoidable, reduce starting dose to 100mg twice daily. M

IMPORTANT SAFETY INFORMATION

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

I INTERACTIONS → Appendix 1: tucatinib

I SIDE-EFFECTS

▶ Common or very common Arthralgia . diarrhoea . epistaxis . hyperbilirubinaemia . nausea . oral disorders . oropharyngeal pain . rash pustular . skin reactions . vomiting . weight decreased

SIDE-EFFECTS, FURTHER INFORMATION Diarrhoea may be severe and associated with dehydration, hypotension, acute kidney injury and death. For management of diarrhoea, consult product literature.

I CONCEPTION AND CONTRACEPTION gFemales of childbearing potential and male patients with a partner of childbearing potential should use effective contraception during treatment and for at least 7 days after last treatment. MSee also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I PREGNANCY gAvoid—toxicity in animal studies. M

See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

I BREAST FEEDING gAvoid during treatment and for at least 7 days after last dose—no information available. M

I HEPATIC IMPAIRMENT

gCaution in severe impairment (risk of increased exposure). MDose adjustments gReduce starting dose to 200mg twice daily in severe impairment. M

I MONITORING REQUIREMENTS

▶gMonitor liver function every 3 weeks or as clinically indicated M—consult product literature.

▶gConsider using alternative markers of renal function if serum creatinine is raised M—consult product literature.

I NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies (April 2022) NICE TA786 Recommended

Scottish Medicines Consortium (SMC) decisions

▶ Tucatinib (Tukysa ®) in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens (January 2022) SMC No. SMC2398 Recommended

I MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

ELECTROLYTES: May contain Potassium, sodium

▶ Tukysa (Seagen U.K. Ltd) A

Tucatinib 50 mg Tukysa 50mg tablets | 88 tabletP £1,968.42 (Hospital only)

Tucatinib 150 mg Tukysa 150mg tablets | 84 tabletP £5,636.84 (Hospital only)

Vandetanib 10-Aug-2021

I DRUG ACTION Vandetanib is a tyrosine kinase inhibitor.

I INDICATIONS AND DOSE

Treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease

▶ BY MOUTH

▶ Adult: 300 mg once daily, for dose adjustment due to side effects—consult product literature

IMPORTANT SAFETY INFORMATION

MHRA/CHM ADVICE: SYSTEMICALLY ADMINISTERED VEGF PATHWAY INHIBITORS: RISK OF ANEURYSM AND ARTERY DISSECTION (JULY 2020)

A European review of worldwide data concluded that systemically administered VEGF pathway inhibitors may lead to aneurysm and artery dissection in patients with or without hypertension. Some fatal cases have been reported, mainly in relation to aortic aneurysm rupture and aortic dissection. The MHRA advises healthcare professionals to carefully consider the risk of aneurysm and artery dissection in patients with risk factors before initiating treatment with vandetanib; any modifiable risk factors (such as smoking and hypertension) should be reduced as much as possible. Patients should be monitored and treated for hypertension as required.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES See Cytotoxic drugs p. 962.

I CONTRA-INDICATIONS Congenital long QT syndrome . QT interval greater than 480 milliseconds

I CAUTIONS Brain metastases (intracranial haemorrhage reported) . electrolyte disturbances . history of torsades de pointes . hypertension . phototoxicity reactions reported (wear protective clothing and/or sunscreen) . risk factors for aneurysm or artery dissection . susceptibility to QTprolongation

CAUTIONS, FURTHER INFORMATION

▶ Monitoring of blood pressure The MHRA advises to monitor blood pressure regularly—consult product literature if hypertension occurs during treatment.

I INTERACTIONS → Appendix 1: vandetanib

I SIDE-EFFECTS

▶ Common or very common Alopecia . anxiety . appetite decreased . asthenia . cerebral ischaemia . cholelithiasis . constipation . corneal deposits . cystitis . dehydration . depression . diarrhoea . dizziness . dry eye . dry mouth . dysphagia . electrolyte imbalance . eye disorders . eye inflammation . fever . gastrointestinal discomfort . gastrointestinal disorders . glaucoma . haemorrhage . headache . hyperglycaemia . hypertension . hypothyroidism . increased risk of infection . insomnia .

lethargy . loss of consciousness . movement disorders . nail disorder . nausea . nephrolithiasis . oedema . pain . photosensitivity reaction . proteinuria . QT interval prolongation . renal impairment . respiratory disorders . sensation abnormal . sepsis . skin reactions . stomatitis . taste altered . tremor . urinary disorders . vision disorders . vomiting . weight decreased

▶ Uncommon Arrhythmias . brain oedema . cardiac arrest . cardiac conduction disorder . cataract . healing impaired . heart failure . malnutrition . pancreatitis . posterior reversible encephalopathy syndrome (PRES) . seizure . urine discolouration

▶ Frequency not known Aneurysm . artery dissection . Stevens-Johnson syndrome

I CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 4 months after treatment.

I PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk. Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

I BREAST FEEDING Avoid—no information available.

I HEPATIC IMPAIRMENT Manufacturer advises avoid if liver function tests exceed specific limits—consult product literature.

I RENAL IMPAIRMENT gAvoid if creatinine clearance less than 30 mL/minute (limited information available).

M

Dose adjustments gConsider reducing starting dose to 200mg if creatinine clearance 30–49 mL/minute (limited information available; consult product literature). MSee p. 21.

I MONITORING REQUIREMENTS Monitor ECG, serum potassium, calcium, magnesium and thyroid stimulating

hormone before treatment, then 1, 3, 6 and 12 weeks after starting treatment and following dose adjustment or interruption, then every 3 months for at least 1 year.

DIRECTIONS FOR ADMINISTRATION Manufacturer advises tablets may be dispersed in half a glass of water by stirring until dispersed (approximately 10 minutes), immediately before drinking (do not crush). After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed. The solution can also be administered via nasogastric or gastrostomy tubes.

PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer vandetanib tablets.

Phototoxicity reactions Patients should be advised to wear protective clothing and/or sunscreen.

Alert card An alert card should be provided.

NATIONAL FUNDING/ACCESS DECISIONS

For full details see funding body website

NICE decisions

▶ Vandetanib for treating medullary thyroid cancer (December 2018) NICE TA550 Not recommended

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Caprelsa (Sanofi Genzyme) A

Vandetanib 100 mg Caprelsa 100mg tablets | 30 tablet P £2,500.00

Vandetanib 300 mg Caprelsa 300mg tablets | 30 tablet P £5,000.00

Vemurafenib 10-Jun-2021

DRUG ACTION Vemurafenib is a BRAF kinase inhibitor.

INDICATIONS AND DOSE

Monotherapy for the treatment of BRAF V600 mutationpositive unresectable or metastatic melanoma

▶ BY MOUTH

▶ Adult: 960 mg twice daily, for dose adjustment due to side effects—consult product literature

IMPORTANT SAFETY INFORMATION

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)

DRESS syndrome has been reported in patients taking vemurafenib. DRESS syndrome starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal.

Patients should be advised to stop taking vemurafenib and consult their doctor immediately if skin rash develops. Treatment with vemurafenib should not be restarted.

MHRA/CHM ADVICE (NOVEMBER 2015): RISK OF POTENTIATION OF RADIATION TOXICITY

Potentiation of radiation toxicity has been reported in patients treated with vemurafenib before, during, or after radiotherapy—use with caution.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES

See Cytotoxic drugs p. 962.

CONTRA-INDICATIONS Wild-type BRAF malignant melanoma

CAUTIONS Electrolyte disturbances . prior or concurrent cancer associated with RAS mutation—increased risk of tumour progression . susceptibility to QT-prolongation

INTERACTIONS → Appendix 1: vemurafenib

SIDE-EFFECTS

▶ Common or very common 7th nerve paralysis . alopecia . appetite decreased . arthralgia . arthritis . asthenia . connective tissue disorders . constipation . cough . diarrhoea . dizziness . eye inflammation . fever . folliculitis . headache . myalgia . nausea . neoplasms . pain . panniculitis . peripheral oedema . photosensitivity reaction .QT interval prolongation . radiation injuries . skin reactions . taste altered . vomiting . weight decreased

▶ Uncommon Liver injury . neutropenia . pancreatitis . peripheral neuropathy . retinal occlusion . severe cutaneous adverse reactions (SCARs) . vasculitis

▶ Rare or very rare Acute tubular necrosis . nephritis acute interstitial

▶ Frequency not known Acute kidney injury

CONCEPTION AND CONTRACEPTION Effective contraception required during for at least 6 months after treatment.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs p. 962.

ı BREAST FEEDING Avoid—no information available.
ı HEPATIC IMPAIRMENT Manufacturer advises caution in moderate to severe impairment (risk of increased exposure)—monitor ECG monthly during the first 3 months of treatment, followed by at least every 3 months thereafter (if QTc interval is prolonged, consult product literature).
ı RENAL IMPAIRMENT gCaution in severe impairment (limited information available). M
ı MONITORING REQUIREMENTS
▶ Monitor ECG and electrolytes before treatment, after one month and following dose adjustment (treatment not

recommended if QT interval greater than 500 milliseconds at baseline).
▶ Monitor liver function before treatment and periodically thereafter.
▶ Monitor for uveitis, iritis and retinal vein occlusion.
▶ Monitor for cutaneous and non-cutaneous squamous cell carcinoma and new primary melanoma before, during and for up to 6 months after treatment—consult product literature.
ı DIRECTIONS FOR ADMINISTRATION Manufacturer advises may be taken with or without food; avoid consistent intake of both daily doses on an empty stomach (may affect absorption).
ı PATIENT AND CARER ADVICE Counselling advised (administration).
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) Patients should be advised to stop taking vemurafenib and consult their doctor immediately if skin rash develops.
ı NATIONAL FUNDING/ACCESS DECISIONS
For full details see funding body website
NICE decisions
▶ Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (updated January 2015) NICE TA269 Recommended with restrictions
Scottish Medicines Consortium (SMC) decisions
▶ Vemurafenib (Zelboraf ®) as monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma (December 2013) SMC No. 792/12 Recommended with restrictions
ı MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Zelboraf (Roche Products Ltd)
Vemurafenib 240 mg Zelboraf 240mg tablets | 56 tabletP
£1,750.00 (Hospital only)