Venetoclax with Obinutuzumab

INDICATION

CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA (SLL) [ICD-10 codes: C91, C83]

First line treatment of patients with previously untreated CLL/SLL [Licensed/NICE approved [TA663] / NB. Different Blueteq forms depending on funding criteria:

- previously untreated CLL/SLL which has a 17p deletion or TP53 mutation (**BLUETEQ** required)
- previously untreated CLL/SLL which does not have a 17p deletion or a TP53 mutation and when chemotherapy with FCR or BR is unsuitable (**BLUETEQ** required)
- previously untreated CLL/SLL which does not have a 17p deletion or a TP53 mutation and when chemotherapy with FCR or BR is suitable (**BLUETEQ** required)

TREATMENT INTENT

Induction and maintenance of remission

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of therapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, cytopenias, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests – FBC, ESR, DAT, U&Es, LDH, G6PD, urate, calcium, magnesium, creatinine, phosphate, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody (HBcAb) and hepatitis B surface antigen Ag (HBsAg), hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. Genetic tests for 17p deletion, TP53 mutation, and IGHV mutation status.
5. Urine pregnancy test – before first cycle of chemotherapy in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy. Ensure the pregnancy declaration is signed to confirm that patient must use effective protection against pregnancy from cycle 1 onwards until 6 months following the completion of venetoclax treatment.
6. ECG +/- ECHO - if clinically indicated.
7. Record performance status (ECOG).
8. Consent and counselling - ensure patient has received adequate verbal and written information regarding their disease, treatment, and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
9. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
10. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
11. **Assess the level of risk of tumor lysis syndrome (TLS)** and provide prophylactic hydration and anti-hyperuricemics accordingly. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8) [Link] [see DRUG REGIMEN (Prevention of TLS), Table 1, 2 and Appendix 1].
12. **For patients at high risk of developing infusion related reactions (IRRs) to obinutuzumab, consider pre-phase dexamethasone**. Dose at Consultant discretion, 4-10mg PO daily for 2 days, starting 48 hours before the 1st dose of obinutuzumab. Pre-phrase steroid is unlikely to be needed beyond this time point. Please discuss with Consultant before given subsequently.
13. Consider withholding antihypertensive treatments 12 hours before, during and for the first hour after the obinutuzumab infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medications.
14. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

CYCLE 1				
Drug	**Day(s)**	**Dose**	**Route**	**Administration details**
Hydration and Pre-medications	**1, 2, 8 & 15**	**See below**		
OBINUTUZUMAB	**1**	100mg	IV	In 100mL sodium chloride 0.9% over at least 4 hours* [**consider slower rate in higher risk of infusion related reactions (IRRs), see below**]
	2	900mg	IV	In 250mL sodium chloride 0.9% (see *INFUSION RATES* below)
	8 & 15	1000mg	IV	In 250mL sodium chloride 0.9% (see INFUSION RATES below)
VENETOCLAX	**22–28**	20mg ONCE DAILY	PO	Dispensed as 10mg tablets. Take in the morning with food*
CYCLE FREQUENCY: every 28 days				

CYCLE 2				
Drug	**Day(s)**	**Dose**	**Route**	**Administration details**
Hydration and Pre-medications	**1**	**See below**		
OBINUTUZUMAB	**1**	1000mg	IV	In 250mL sodium chloride 0.9% (see INFUSION RATES below)
VENETOCLAX	**1–7**	50mg ONCE DAILY	PO	Dispensed as 50mg tablets (50mg dose) and 100mg tablets (100mg, 200mg and 400mg doses). Take in the morning with food*
	8–14	100mg ONCE DAILY		
	15–21	200mg ONCE DAILY		
	22–28	400mg ONCE DAILY		
CYCLE FREQUENCY: every 28 days				

CYCLES 3–6				
Drug	**Day(s)**	**Dose**	**Route**	**Administration details**
Hydration and Pre-medications	**1**	**See below**		
OBINUTUZUMAB	**1**	1000mg	IV	In 250mL sodium chloride 0.9% (see INFUSION RATES below)
VENETOCLAX	**1–28**	400mg ONCE DAILY	PO	Dispensed as 100mg tablets. Take in the morning with food*
CYCLE FREQUENCY: every 28 days				

CYCLES 7–12				
Drug	**Day(s)**	**Dose**	**Route**	**Administration details**
VENETOCLAX	**1–28**	400mg ONCE DAILY	PO	Dispensed as 100mg tablets. Take in the morning with food*
CYCLE FREQUENCY: every 28 days				

DURATION: 12 cycles

***See DOSE MODIFICATIONS below due to Venetoclax drug interactions** – NB. Patients should avoid consuming grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

DELAYED OR MISSED DOSES

- **Obinutuzumab.** If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; no doses should be omitted. If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, requiring delay of treatment, these doses should be given after resolution of toxicity and all subsequent visits, and the start of Cycle 2 should be shifted to accommodate for the delay in Cycle 1. Then original dosing schedule should be maintained for subsequent doses.

  In case of obinutuzumab treatment delays, note the maximum treatment duration of venetoclax in this indication is until day 28 of the 12th cycle of treatment i.e., the maximum duration of full dose venetoclax treatment is for 45 weeks, consisting of 1 week from cycle 1 day 22 followed by 11 cycles of 4-weekly cycles of venetoclax in cycles 2-12.

- **Venetoclax.** Missed venetoclax dose within 8 hours of the time it is usually taken, should be taken as soon as possible on the same day. If a dose is missed by more than 8 hours, it should be omitted, and the usual dosing schedule resumed the following day. If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

PREVENTION OF INFUSION RELATED REACTIONS (IRRs) to OBINUTUZUMAB

Risk factors for developing severe IRRs at Cycle 1 Day 1: high tumour burden, high circulating lymphocyte count [> 25 x 10^9/L], renal impairment (CrCl < 50 mL/min), and both Cumulative Illness Rating Scale (CIRS) > 6 and CrCl < 70 mL/min

PRE-MEDICATIONS

Pre-meds required **(at least 1 hour before obinutuzumab)**	**Cycle 1 Day 1 & Day 2**	**Subsequent infusions Cycle 1 Days 8 & 15 and Cycles 2–6**		
	All Patients	**Patients without any IRRs symptoms**	**Patients with grade 1 or 2 (mild to moderate) IRRs** with previous infusions	**Patients with grade 3 (severe) IRRs** with previous infusion OR with lymphocyte count >25 x10^9/L prior to next treatment
Dexamethasone 20mg IV[a]	√			√
Paracetamol 1g PO	√	√	√	√
Loratadine 10mg PO	√		√	√
Famotidine 40mg PO	√			√

[a] *Equivalent to 16.5mg dexamethasone base*

INFUSION RATES

Cycle number (Obinutuzumab dose)	**Infusion rates** at cycle 1 and subsequent cycles providing no IRRs with previous obinutuzumab doses. Do not increase infusion rates in case IRRs occur	
	Additional risk factors for severe IRRs (see above)	
	Yes	**No**
Cycle 1 Day 1 (100mg)	6mg/hour for 1 hour, 12mg/hour for 1 hour, then 24mg/hour until the end of infusion (Total infusion duration: 5 hrs 25 min)	25mg/hour. Do not increase the infusion rate. (Total infusion duration 4 hrs)
Cycle 1 Day 2 (900mg)	50mg/hour for 30 minutes, then increase rate in 50mg/hour increments every 30 min. to max. rate 400mg/hour (Total infusion duration 4 hrs)	
Cycle 1 Day 8 onwards (1000mg)	100mg/hour for 30 minutes, then increase rate in 100mg/hour increments every 30 min. to max. rate 400mg/hour (Total infusion duration ~3 hrs 15 min)	

PREVENTION OF TUMOUR LYSIS SYNDROME (TLS)

Both obinutuzumab and venetoclax carry the risk of TLS. Debulking with obinutuzumab before starting venetoclax is likely to reduce the TLS risk, therefore it is recommended to assess TLS risk before first obinutuzumab dose (Table 1), and re-assess after 3 weeks, before the first venetoclax dose (Table 2), adjusting TLS management and monitoring accordingly. TLS risk assessment should include lymph nodes (LN) size, absolute lymphocyte count (ALC), and CrCl (calculated creatinine clearance). Splenomegaly may further increase TLS risk although this is not part of the formal scoring system.

Table 1. TLS RISK ASSESSMENT Pre-cycle 1 (pre 1st OBINUTUZUMAB dose)

	Low tumour burden	**Medium tumour burden**	**High tumour burden**
TLS risk factors	All LN < 5cm (baseline)	Any LN 5cm to < 10cm (baseline)	Any LN ≥ 10cm (baseline)
TLS management	Oral hydration **AND** Allopurinol	Oral or IV hydration **AND** Allopurinol	Oral hydration **AND** IV hydration **AND** Allopurinol **AND / OR** Rasburicase for elevated uric acid (>8 mg/dL)
TLS monitoring	**OUTPATIENT**	**OUTPATIENT**	**AMBULATORY CARE* / INPATIENT**
Cycle 1 Day 1 Cycle 1 Day 2 Cycle 1 Day 8 Cycle 1 Day 15	Pre-dose	Pre-dose	Pre-dose

Table 2. TLS RISK ASSESSMENT Cycle 1 Week 3 (pre 1st VENETOCLAX dose)

	Low tumour burden	**Medium tumour burden**	**High tumour burden**
TLS risk factors	All LN < 5cm (baseline) **AND** ALC < 25 x 10^9/L (pre-Venetoclax)	Any LN 5cm to < 10cm (baseline) **OR** ALC ≥ 25 x 10^9/L (pre-Venetoclax)	Any LN ≥ 10cm (baseline) **OR** Any LN ≥ 5cm (baseline) and ALC ≥ 25 x 10^9/L (pre-Venetoclax)
TLS management	Oral hydration **AND** Allopurinol	Oral or IV hydration **AND** Allopurinol	Oral hydration **AND** IV hydration **AND** Allopurinol **AND / OR** Rasburicase for elevated uric acid (>8 mg/dL)
TLS monitoring	**OUTPATIENT**	**OUTPATIENT** [consider monitoring as high risk when CrCl<80mL/min]	**AMBULATORY CARE* / INPATIENT**
Cycle 1 Day 22 Cycle 2 Day 1	Pre-dose, 6-8, 24 hours	Pre-dose, 6-8, 24 hours	Pre-dose, 4, 8, 12, 24 hours
Cycle 2 Day 8 Cycle 2 Day 15 Cycle 2 Day 22	Pre-dose	Pre-dose	Pre-dose, 6-8, 24 hours

See Appendix 1 for Ambulatory Care eligibility and exclusion criteria.

CONCURRENT MEDICATIONS

TLS prophylaxis	**Hydration** throughout treatment**:** 2-3L/day PO fluids starting 1-2 days before Cycle 1 Day 1. Medium/High TLS risk: Additional IV fluids as per Table 1 and 2 above. Total PO+IV fluids ~3L/m^2/day, to maintain urine output >100mL/m^2/hour)
	Allopurinol: 300mg/day starting 2 days before Cycle 1 Day 1 (reduce dose to 100mg if CrCl<20 mL/min), continue for 8 weeks (until the end of venetoclax ramp-up dosing). Allopurinol should be omitted on days of rasburicase.
	Rasburicase:. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8) [Link]. High TLS risk with elevated uric acid (>8 mg/dL): consider before first dose(s) of obinutuzumab in cycle 1 and before each first venetoclax escalation dose (cycle 1 day 22, and cycle 2 days 1, 8, 15, and 22)
Antiviral prophylaxis	**Aciclovir**: 200mg three times a day for duration of treatment and for 3 months after completion

EMETIC RISK: Low

DOSE MODIFICATIONS

OBINUTUZUMAB

Dose modifications are not recommended. In case of IRRs, delay or stop treatment and/or adjust infusion rates as per table below.

IRRs grade	**Recommendations** on infusion rates in case IRRs
Grade 4 (life threatening)	▪ Infusion must be stopped and therapy permanently discontinued.
Grade 3 (severe)	▪ Infusion must be temporarily stopped and symptoms treated. ▪ Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred). ▪ If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. ▪ Cycle 1 day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. ▪ If the patient experiences a second occurrence of a grade 3 IRR, the infusion must be stopped and therapy permanently discontinued.
Grade 1-2 (mild to moderate)	▪ The infusion rate must be reduced and symptoms treated. ▪ Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred). ▪ If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. ▪ The day 1 (cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Renal impairment*	CrCl ≥ 30ml/min	No dose adjustment required.
	CrCl < 30mL/min	No data. In current practice dose adjustment is not recommended.
Hepatic impairment	No data. No need for dose adjustment is expected.	

NB. Patients with renal impairment CrCl < 50mL/min are more at risk of IRRs, neutropenia and thrombocytopenia.

VENETOCLAX

Hematological Toxicities		
Grade 3 or 4 neutropenia (ANC < 1 x10^9/L) with infection or fever; or Grade 4 hematological toxicities except lymphopenia (e.g., ANC <0.5 x10^9/L or Plt < 25 x10^9/L)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 3 below when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the Consultant discretion.

Non-hematological toxicities		
Tumor Lysis Syndrome (blood chemistry changes or symptoms suggestive of TLS)	Any occurrence	Withhold the next day's dose. If resolved within 24 – 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve resume at a reduced dose (see Table 3 below) and discuss with Consultant. If rapid dose escalation is required due to progressive disease, patients have to be admitted for IV hydration and management of TLS.
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 3 below).
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 3 below when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at Consultant discretion.

Drug interactions*	
Strong CYP3A inhibitors	Avoid concomitant use during venetoclax initiation and dose-titration phase. Consider alternative treatments. If patient requires use of these medications after titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
Moderate CYP3A inhibitors and P-gp inhibitors	Avoid concomitant use during venetcolax initiation and dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor or P-gp inhibitor must be used, reduce the initiation and titration doses of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

**See Appendix 2 for a list of CYP3A and P-gp inhibitors and inducers*

Renal impairment*	CrCl ≥ 30mL/min	No dose adjustment required.
	CrCl < 30mL/min or dialysis	No information available. Clinical decision.
Hepatic impairment	Mild-Moderate (Child Pugh A/B)	No dose adjustment required. Patients with moderate impairment should be closely monitored for toxicity.
	Severe (Child-Pugh C)	Reduce dose by 50%. Monitor closely.

***Consider increased risk of TLS in patients with CrCl < 80mL/min.** At discretion of the treating Consultant, more intensive TLS prophylaxis and increased TLS monitoring may be recommended.*

Table 3. Venetoclax dose modifications for toxicity

Dose at interruption	400mg	300mg	200mg	100mg	50mg	20mg
Dose at re-starting[a]	300mg	200mg	100mg	50mg	20mg	10mg

[a] Continue the reduced dose for 1 week before increasing the dose

INVESTIGATIONS

Weekly during titration phase, then reduce as appropriate.

- FBC
- TLS bloods as per Table 1 and 2 above, including creatinine and U&Es: uric acid, potassium, phosphate, and calcium
- Liver function tests
- Glucose

RESTAGING

Clinical response should be assessed on a monthly basis for the first 3 months. Re-image at approximately 3 and 12 months on treatment as per Consultant discretion.

CONTRAINDICATIONS

Renal failure or other significant co-morbidities that increase the risk of TLS. Patients should be treated in centers with experience in managing TLS. Concomitant use of strong CYP3A inhibitors at initiation and during the venetoclax dose-titration phase.

EXTRAVASATION RISK

Obinutuzumab: neutral
Venetoclax (oral): not applicable

WARNINGS AND SPECIAL PRECAUTIONS – MHRA advice for healthcare professionals:

Venetoclax

- TLS risk must be assessed based on multiple factors, including tumour burden, comorbidities (particularly reduced renal function) and splenomegaly. For all patients, it is important to strictly adhere to the dose-titration schedule and to the measures to minimise the risk of TLS.
- Patients should be advised to stop taking venetoclax and seek medical attention immediately if any of the symptoms of TLS occur (fever or chills, nausea or vomiting, confusion, feeling short of breath, irregular heartbeat, dark or cloudy urine, feeling unusually tired, muscle pain or uncomfortable joints, fits or seizures, abdominal pain and distension).
- Patients should be given the alert card [Link] to be carried with them at all times and shared with their healthcare professionals involved in their care.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with Pharmacist and refer to SmPC for full details)

Venetoclax–Obinutuzumab:

- The most common grade 3 and 4 adverse events in the phase 3 trial[1] included: neutropenia (52%), thrombocytopenia (13%), and infections (17.5%). Other common adverse events reported included (≥10%):anemia (16%), IRRs (44%), diarrhea (27%), nausea (18%), pyrexia (22%), fatigue (15%), cough (16%).
- The most common grade 3 and 4 adverse events in the phase 3 trial[1] included: neutropenia (52%), thrombocytopenia (13%), and infections (17.5%). Other common adverse events reported include (≥10%): anemia (16%), IRRs (44%), diarrhea (27%), nausea (18%), pyrexia (22%), fatigue (15%), cough (16%).
- The most common serious adverse events in the phase 3 trial[1] included (≥2%): pneumonia (4.7%), febrile neutropenia (5.2%), IRRs (4.2%), pyrexia (3.8&).
- **Infusion-Related Reactions (IRRs):** rashes, allergic and anaphylactic reactions or cytokine release syndrome (dyspnoea, bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria and angio-oedema).

TREATMENT RELATED MORTALITY

<1%

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Sara Castro and Nadjoua Maouche, Haematology Pharmacists	New Document	December 2020	1.0	Dec 2021
Donna Constantine, Haematology Pharmacist	Addition of ambulatory details and ambulatory eligibility criteria	January 2021	1.1	May 2021
Lymphoma protocol review	TLS risk and other updates according to latest venetoclax & obinutuzumab SmPC. Formatting.	June 2021	1.2	
Natalia Czub and Yen Lim, Haematology Pharmacists, CLL Quality meeting review	IRRs prophylaxis, TLS risk assessment and management updated, General formatting	September 2022	2.0	September 2024
Natalia Czub, Haematology Pharmacist, NSSG Lymphoma Group	Pre-assessment (pre-phase steroids), TLS prophylaxis updated. General formatting.	July 2023	2.1	July 2025

APPENDIX 1

AMBULATORY TREATMENT

This regimen is eligible for treatment within a specialized ambulatory unit (e.g., Oxford Cancer Ambulatory Care Unit) for moderate or high-risk TLS as an alternative to inpatient admission. Specific patient restrictions apply, as stated below, in addition to usual eligibility criteria outlined in local ambulatory cancer treatment policy.

Exclusions to treatment:

- Age > 80 years or significant frailty.
- Creatinine clearance (CrCl) < 30mL/min or dependence on dialysis.
- Clinically significant cardiac impairment.
- G6PD deficiency.
- Co-morbid conditions needing careful fluid management e.g., diabetes insipidus.
- Drug-interactions (unavoidable) having potential to need careful adjustment and monitoring of medications for other co-morbid conditions. Consult pharmacist.
- Expected poor compliance with treatment directions/monitoring requirements.

Patients not eligible for this pathway should be planned for inpatient admission during titration. Ambulatory treatment involves a number of visits and may not be suitable for all patients.

Important notes:

- Consent should be given for ambulatory treatment at clinic assessment. An electronic referral form for Ambulatory Care treatment should be completed.
- Patients should be **prescribed and supplied allopurinol in advance,** ideally in clinic, to allow treatment start 2 days prior to venetoclax cycle 1, day 1. They should be advised to omit this on the day of venetoclax when rasburicase will be given.
- Patients will receive a pre-assessment telephone call from ambulatory nurse to confirm arrangements and explain hydration/fluid balance.
- **Patients should receive intravenous hydration (approximately 1 – 1.5L over 8 hours at a rate of 150ml/min) on the day of venetoclax dose escalation** during their stay in the unit and be advised to continue with oral hydration when discharged home.
- Venetoclax take-home supply should remain on the unit and not be given to the patient until day 2 post-escalation bloods have been reviewed for TLS.

APPENDIX 2

CYP3A INHIBITORS/INDUCERS AND P-GP/BCRP INHIBITORS/SUBSTRATES^.

Note this list is not conclusive. Consult with a Pharmacist and refer to the product SmPC.

CYP3A Inhibitors	Strong	clarithromycin, itraconazole, ketoconazole, lopinavir, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, voriconazole
	Moderate	aprepitant, ciprofloxacin, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil
CYP3A Inducers	Strong	carbamazepine, phenytoin, rifabutin, rifampin, St. John's Wort
	Moderate	bosentan, efavirenz, etravirine, modafinil, oxcarbazepine
P-gp Inhibitors		amiodarone, azithromycin, captopril, carvedilol, ciclosporin, felodipine, quinidine, ranolazine, ticagrelor
BCRP Inhibitors		ciclosporin, geftinib
Substrates of P-gp		colchicines, dabigatran etexilate, digoxin, fexofenadine, loperamide, ranolazine, saxagliptin, sirolimus, tolvaptan
Substrates of BCRP		methotrexate, rosuvastatin, sulfasalazine

^*https://clinicaltrials.gov/ct2/show/NCT02910583*