TDM monograph Bictegravir

Synonyms: Biktarvy

Summary

Indication:	**HIV infection** Indication TDM: Prevention of virological failure
Sample material:	EDTA plasma (without gel)
Time of sampling:	Trough sample, i.e. prior to next dose
Storage conditions:	2-8 ºC (during transport) / -40 ºC (storage until analysis)
Interpretation:	Target trough concentration: > 0.76 mg/L
Evidence level:	4

Contents

Introduction

Bictegravir (BIC) is formulated together with emtricitabine/tenofovir alafenamide fumarate (FTC/TAF) as a fixed dose combination (Biktarvy®). The adult FDC contains 50/200/25 mg of BIC/FTC/TAF; the pediatric formulation 30/120/15 mg.
BIC is not available as a separate formulation, making dose adjustments difficult.

Dosing guidelines

HIV

BIC is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1)(1).

The adult dose is 1 film-coated tablet of the adult formulation QD (50/200/25mg)

Dosing guidelines in children and adolescents

Pediatric patients at least 2 years of age and weighing 14-25kg: 1 pediatric FDC QD (30/120/15mg).
Children weighing 25kg or more can also take the adult FDC (50/200/25)(2)

Dosing guidelines in patients with altered pharmacokinetics

No dose adjustment of BIC is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIC has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), therefore Biktarvy is not recommended for use in patients with severe hepatic impairment.

No dose adjustment of BIC is required in patients weighing ≥ 35 kg with estimated creatinine clearance (CrCl) ≥ 30 mL/min. No dose adjustment of BIC is required in adult patients with end stage renal disease (estimated creatinine clearance < 15 mL/minute) who are receiving chronic haemodialysis.

On days of haemodialysis, BIC should be administered after completion of haemodialysis treatment.

See (3)
Page 84: Dose adjustment of ARVs for impaired renal function
Page 93: Dose adjustment of ARVs for impaired hepatic function

Indications/Criteria for TDM

The primary indication for TDM of BIC is the prevention of virological failure. Other potential indications for TDM can be:

- Potential drug concentration-related toxicity
- Special patient populations (pregnancy, children)
- Drug-drug interactions
- Suspicion of nonadherence
- Etc.

Reference values

Target trough concentration (for more information, see below):
> 0.76 mg/L

Efficacy

In a Phase Ib placebo-controlled study (4) in either treatment-naive or INSTI-naive patients, 4 different BIC doses were tested for 10 days as monotherapy. The doses used were 5 mg, 25 mg, 50 mg and 100 mg, all QD. This showed that increasing BIC exposure resulted in increased virologic response. The protein binding adjusted (pa) IC95 is 0.162 mg/L (5).

In several phase III studies, pharmacokinetic substudies have been performed with the registered BIC dose of 50mg once daily. The trough levels observed in these ranged between 2.0-2.6 mg/L. .

The FDA's pharmacometric review has modeled BIC. Based on this model, the percentage of patients with a virological response was examined. They saw no difference between the lowest and highest quartile for trough levels of BIC. The lowest quartile included 149 patients, of which 148 patients had a viral load < 50 copies/ml. The lowest measured trough level in the lowest quartile was 0.76 mg/L.

A phase 1 study (6) between BIC and rifampicin in 26 healthy volunteers per group looked at the effect rifampicin 600mg QD on the pharmacokinetics of BIC 50mg BID (cohort 1) compared to BIC 50mg QD without rifampicin (cohort 2). The mean trough level of BIC in combination with rifampicin was 0.61 mg/L, while the mean trough level without rifampicin was 3.07 mg/L. The trough level of BIC is thus reduced by 80% in combination with rifampicin, despite the dose increase to 50 mg BID. These low concentrations of BIC when combined with rifampicin were considered undesirable and the combination of rifampicin and BIC is therefore currently contraindicated. It can be deduced from this that trough levels of 0.61 mg/L or lower are considered undesirable.

Based on the above information, it is currently concluded that the minimum trough level should be above 0.76 mg/L, which corresponds to the lowest value from the 1st quartile of BIC trough levels. Levels between 0.162 – 0.76 mg/l may also be effective. There is currently a phase IIB study ongoing in TB/HIV-infected patients were double dosed BIC/TAF/FTC is combined with rifampicin that will help in assessing the minimum effective concentration of BIC as trough levels of BIC will likely fall in that range of 0.162-0.76

mg/L.

Relationship with occurrence of side effects

A phase 1b study (4) with 4 different doses of BIC, 5 mg, 25 mg, 50 mg and 100 mg for 10 days, showed no differences in the incidence or severity of the side effects between the different doses.

A phase 1 study in 15 patients looked at potential interactions between bictegravir and other drugs and the effect on pharmacokinetics (7). The interaction between darunavir/cobicistat and bictegravir has been studied in one cohort. The mean steady-state trough level of bictegravir was 4.02 mg/L without darunavir/cobicistat and 8.49 mg/L with this combination. The mean AUC increased by 74%. There was no indication for more toxicity if the combination was used. A clinical study (8) in nine patients using the same regimen described a 26% increase in AUC when compared to historical controls.
In terms of side effect profile, bictegravir is similar to dolutegravir.

Toxicity

In clinical studies of treatment-naïve patients receiving BIC/FTC/TAF, the most frequently reported adverse reactions in the double-blind phase (Week 144) were headache (5%), diarrhoea (5%) and nausea (4%)(1)

Sampling & storage conditions

A TDM sample should be taken in an EDTA tube without gel. BIC is sensitive to light. TDM blood samples should be processed within 30 minutes, or protected from light. Transport to an external laboratory should be at 2-8 ºC. Samples should be stored at -40 ºC pending analysis.

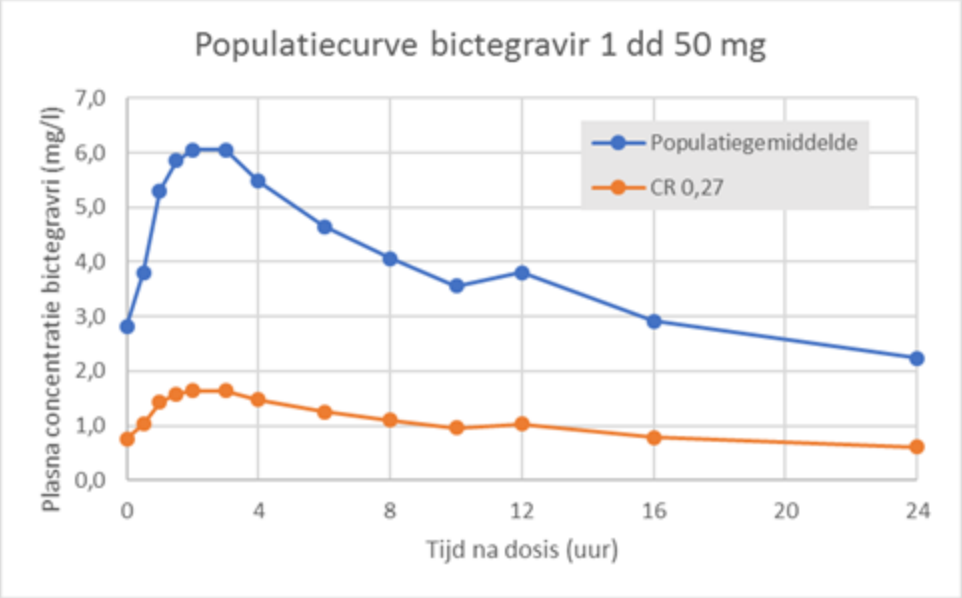
Additional information concerning the interpretation of results

Trough levels should be > 0.76 mg/L in treatment-naive patients

If the level is < 0.76 mg/L: discuss the importance of adherence to therapy, check co-medication for interactions; recommend taking BIC with food.

Time(hr)	Concentration (mg/L)	CR 0,27
0,0	2,82	0,76
0,5	3,80	1,03
1,0	5,30	1,43
1,5	5,86	1,58
2,0	6,05	1,63
3,0	6,05	1,63
4,0	5,48	1,48

6,0	4,64	1,25
8,0	4,07	1,10
10,0	3,56	0,96
12,0	3,80	1,03
16,0	2,92	0,79
24,0	2,24	0,60



Background information [extended]

Pharmacodynamics

BIC is an integrase strand transfer inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. BIC has activity against HIV-1 and HIV-2.

Pharmacokinetics

Tmax after oral administration is 2-4h post-dose. A moderate-to-high fat meal increased BIC AUC by 24%. However, because absorption on an empty stomach is already adequate, BIC can be taken without regard to intake of food.

BIC is highly bound to plasma proteins (>99%).

BIC is metabolized through CYP3A and UGT1A1. Elimination of unchanged BIC in the urine is minimal (1%).

The elimination half-life of BIC is 17h.

Pharmacogenetics

Population analyses using pooled pharmacokinetic data from adult studies
did not identify any clinically relevant differences due race on the exposures of BIC (1).

Interactions

See: (9)

www.hiv-druginteractions.org

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	Protein binding	Tmax (h)	Ref.
HIV-infected patients				17	>99.0%	2-4	(1)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
HIV-infected patients	FDA	1.26-2.88	7.0-9.6	NR	0.453	(7)

Literature

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Colophon

This guideline has been constituted by David Burger, PharmD, PhD
Date: [May 14, 2024]

Appendices

Not applicable

Revision

This guideline has been revised by David Burger, PharmD, PhD under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

The guidelines was updated based on most recent literature and translated to English
Date: [May 14, 2024]