אוגוסט 2019

הודעה על תחילת שיווק אצווה מסחרית ועדכון עלונים:

Biktarvy film coated tablets

(bictegravir / emtricitabine / tenofovir alafenamide fumarate)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם כי בימים אלה חל שיווק אצווה מסחרית לתכשיר בנדון. כמו כן, חל עדכון בעלון לרופא ובעלון לצרכן של התכשיר בנדון ביוני 2019 המובא לידיעתכם.

ההתוויה הרשומה לתכשיר בישראל:

Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir**.**

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#/byDrug

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל.

התכשיר משווק ע"י סל"א ללא צורך בהגשת 29ג'.

בברכה,

מריה חורגין

רוקחת ממונה

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4.8 Undesirable effects

Summary of the safety profile

The assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies with Biktarvy and from post-marketing experience. In clinical studies of treatment-naive patients receiving Biktarvy through ~~48~~ 96 weeks, the most frequently reported adverse reactions were headache (5%), diarrhoea (5%) and nausea (4%).

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Table 2: Tabulated list of adverse reactions[1]

Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	
Uncommon:	angioedema[2,3,4], rash, pruritus, urticaria[4]

[1] With the exception of angioedema, ~~and~~ anaemia and urticaria (see footnotes 2,3 and 4), all adverse reactions were identified from clinical studies of emtricitabine+tenofovir ~~alafenamide~~ alafenamide-containing products. The frequencies were derived from Phase 3 Biktarvy clinical studies in treatment-naïve patients through ~~48~~ 96 weeks (GS-US-380-1489 and GS-US-380-1490).

[2] This adverse reaction was not observed in the clinical studies of emtricitabine+tenofovir alafenamide containing products but identified from clinical studies or post-marketing experience for emtricitabine when used with other antiretrovirals.

[3] This adverse reaction was identified through post-marketing surveillance for emtricitabine-containing products. ~~but was not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies (n=1563).~~

[4] This adverse reaction was identified through post-marketing surveillance for tenofovir alafenamide-containing products.

Description of selected adverse reactions

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Changes in serum creatinine

Bictegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine, however these changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week ~~48~~96. In Studies GS-US-380-1489 and GS-US-380-1490, median (Q1, Q3) serum creatinine increased by 0.~~10~~09 (0.~~03~~01, 0.~~17~~16) mg/dL (8.0 [0.9, 14.1] µmol/L), 0.~~11~~09 (0.03, 0.~~18~~17) mg/dL (8.0 [2.6, 15.0] µmol/L), and 0.11 (0.04, 0.~~19~~18) mg/dL (9.7 [3.5, 15.9] µmol/L) from baseline to Week ~~48~~ 96 in the Biktarvy, abacavir/dolutegravir/lamivudine, and dolutegravir+emtricitabine/tenofovir alafenamide groups, respectively. There were no discontinuations due to renal adverse events through Week ~~48~~ 96 in patients administered Biktarvy in clinical studies.

Changes in bilirubin

In Studies GS-US-380-1489 and GS-US-380-1490, total bilirubin increases were observed in ~~12~~15% of treatment-naïve patients administered Biktarvy through Week ~~48~~96. Increases were primarily Grade 1 (~~9~~11%) and Grade 2 (~~3~~4%) (≥1.0 to 2.5 x Upper Limit of Normal [ULN]), and were not associated with hepatic adverse reactions or other liver related laboratory abnormalities. Four patients administered Biktarvy (1%) had grade 3 bilirubin increases that were not considered related to study drug. There were no discontinuations due to hepatic adverse events through Week ~~48~~ 96 in Biktarvy clinical studies.

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5.1 Pharmacodynamic properties

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In treatment-naïve (Studies GS-US-380-1489 and GS-US-380-1490) and virologically-suppressed patients (Studies GS-US-380-1844 and GS-US-380-1878), no patient receiving Biktarvy had HIV-1 with treatment emergent genotypic or phenotypic resistance to bictegravir, emtricitabine, or tenofovir alafenamide in the final resistance analysis population (n=~~13~~ 10 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, Week 96 (treatment naïve studies only) or early study drug discontinuation.~~). At the time of study entry, six treatment-naïve patients and one virologically-suppressed patient receiving Biktarvy had pre-existing INSTI resistance-associated~~

~~mutations (6 subjects with T97A and one treatment-naïve subject with Q148H + G140S); all had HIV-1 RNA < 50 copies/mL at Week 48.~~ At the time of study entry, one treatment-naïve patient had pre-existing INSTI resistance-associated mutations Q148H + G140S and had HIV-1 RNA < 50 copies/mL at Week 4 through Week 96. In addition, 6 patients had the pre-existing INSTI resistance-associated mutation T97A; all had HIV-1 RNA < 50 copies/mL at Week 96 or the last visit.

Clinical data

The efficacy and safety of Biktarvy in HIV-1 infected, treatment-naïve adults are based on 48-week and 96-week data from two randomized, double-blind, active-controlled studies, GS-US-380-1489 (n=629) and GS-US-380-1490 (n=645).

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Table 3: Pooled Virologic Outcomes of Studies GS-US-380-1489 and GS-US-380-1490 at Weeks 48[a] and 96[b] ~~in Treatment-Naïve Patients~~[a]

	Week 48			Week 96		
	B/F/TAF (n=634)[~~b~~c]	**ABC/DTG/ 3TC (n=315)[~~c~~d]**	**DTG + F/TAF (n=325)[~~d~~e]**	**B/F/TAF (n=634)[c]**	**ABC/DTG /3TC (n=315)[d]**	**DTG + F/TAF (n=325)[e]**
HIV-1 RNA < 50 copies/mL	91%	93%	93%	86%	90%	86%
Treatment Difference (95% CI) B/F/TAF vs. Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)	-	-3.8% (-8.2% to 0.6%)	-0.4% (-5.0% to 4.3%)
HIV-1 RNA ≥ 50 copies/~~mL~~[e] mL[f]	3%	3%	1%	3%	2%	3%
No Virologic Data at Week 48 or 96 Window	6%	4%	6%	12%	8%	11%
Discontinued Study Drug Due to AE or ~~Death~~[f] Death[g]	<1%	1%	1%	1%	2%	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/~~mL~~[g] mL[h]	4%	3%	4%	9%	5%	7%
Missing Data During Window but on Study Drug	2%	<1%	1%	1%	1%	1%
Proportion (%) of Patients with HIV-1 RNA < 50 copies/mL by Subgroup[~~h~~i]						
By Baseline Viral Load						
≤ 100,000 copies/mL	92%	94%	93%	87%	91%	86%
> 100,000 copies/mL	87%	90%	94%	82%	84%	87%
By Baseline CD4+ Cell Count						
< 200 cells/mm^3	90%	81%	100%	83%	81%	94%
≥ 200 cells/mm^3	91%	94%	92%	86%	91%	86%
HIV-1 RNA < 20 copies/mL	85%	87%	87%	80%	85%	80%

ABC=abacavir DTG=dolutegravir 3TC=lamivudine F/TAF=emtricitabine/tenofovir alafenamide

a Week 48 window was between Day 295 and 378 (inclusive).

b Week 96 window was between Day 631 and 714 (inclusive).

~~b~~c Pooled from Study GS-US-380-1489 (n=314) and Study GS-US-380-1490 (n=320).

~~c~~d Study GS-US-380-1489

~~d~~e Study GS-US-380-1490

~~e~~f Includes patients who had ≥ 50 copies/mL in the Week 48 or 96 window; patients who discontinued early due to lack or loss of efficacy (n=0); patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of

efficacy (B/F/TAF n=12 and 15; ABC/DTG/3TC n=2 and 4; DTG+F/TAF n=3 and 4, at Weeks 48 and 96, respectively) and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

~~f~~g Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

~~g~~h Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g. withdrew consent, loss to follow-up, etc.

~~h Patients who had ≥ 50 copies/mL in the Week 48 window included patients who discontinued early due to lack or loss of efficacy (n=0), and patients who discontinued for reasons other than an AE, death or lack or loss of efficacy (B/F/TAF n=12; ABC/DTG/3TC n=2; DTG+F/TAF n=3), and at the time of discontinuation had a viral value of ≥ 50 copies/mL.~~

B/F/TAF was non-inferior in achieving HIV-1 RNA < 50 copies/mL at both Weeks 48 and 96 when compared to abacavir/dolutegravir/lamivudine and to dolutegravir+emtricitabine/tenofovir alafenamide, respectively. Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, baseline viral load, baseline CD4+ cell count, and region.

In Studies GS-US-380-1489 and GS-US-380-1490, the mean increase from baseline in CD4+ count at Week ~~48~~ 96 was ~~207~~262, ~~229~~288, and ~~201~~ 281 cells/mm^3 in the pooled B/F/TAF, abacavir/dolutegravir/lamivudine, and dolutegravir+emtricitabine/tenofovir alafenamide groups, respectively.

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Patients co-infected with HIV and HBV

The number of patients co-infected with HIV and HBV treated with B/F/TAF is limited. In Study GS-US-380-1490, ~~7 of~~ 8 patients with HIV/HBV co-infection at baseline ~~who~~ were randomized to receive B/F/TAF. At Week 48, 7 patients were HBV suppressed (HBV DNA < 29 IU/mL) and had HIV-1 RNA < 50 copies/mL ~~at Week 48~~. ~~One~~ patient had missing HBV DNA data at Week 48. At Week 96, 4 patients were HBV suppressed and had HIV-1 RNA < 50 copies/mL. Four patients had missing HBV DNA data at Week 96 (one lost to follow-up from Week 48, 1 lost to follow-up after Week 72, 1 with missing HBV data but HIV-1 RNA < 50 copies/mL, and 1 with missing data in Week 96 window).

העדכונים המהותיים בעלון לצרכן:

2. לפני השימוש בתרופה

~~מטופלים הנוטלים ביקטארווי למשך תקופה ארוכה עלולים לפתח בעיות בכליות.~~

על אף כי לא נצפו בעיות בכליות בקרב מטופלים שנטלו ביקטארווי, קיימת אפשרות כי תחווה בעיות בכליות בגלל נטילת ביקטארווי למשך תקופה ארוכה.

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4.תופעות לוואי

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תופעות לוואי שאינן שכיחות

(עשויות להופיע אצל עד 1 מתוך 100 אנשים)

- ....
- *סרפדת (אורטיקריה)*