TEPMETKO®
Tepotinib 225 mg

2024/3

Tepmetko (Tepotinib),

Film coated tablets

רופא/ה, רוקח/ת וצוות רפואי נכבדים,

אנו מבקשים להודיעכם כי העלון לרופא והעלון לצרכן של התכשיר Tepmetko עודכנו.

<u>ההתוויה המאושרת:</u>

TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring a MET tyrosine kinase receptor exon 14 (METex14) skipping mutation.

<u>השינויים בעלון לרופא הינם</u> (טקסט שנוסף מופיע עם <u>קו תחתון</u>, טקסט שנמחק מופיע עם ~~קו חוצה~~):

Special dosage instructions-
Elderly patients
No dose adjustment is necessary in patients aged 65 years and above (see section Pharmacokinetics). Of <u>313</u> ~~255~~ patients with METex14 skipping alterations in the VISION study, 79% were 65 years or older, and 8% were 85 years or older.

Mode of administration
Administration to patient who have difficulty swallowing solids
<u>If the patient is unable to swallow, the tablets can be dispersed in 30 mL of non-carbonated water. No other liquids should be used or added. Drop the tablets in a glass with water without crushing, stir until the tablets dispersed into small pieces (the tablet will not completely dissolve) and swallow the dispersion immediately together with food. Rinse with additional 30 mL to ensure that no residues remain in the glass and drink immediately.</u>
<u>If an administration via a naso-gastric tube (with at least 8 French gauge) is required, disperse the tablets in 30 mL of non-carbonated water as described above. Administer the 30 mL of dispersion immediately together with food as bolus as per naso-gastric tube manufacturer's instructions. Immediately rinse twice with 30 mL of non-carbonated water each to ensure that no residues remain in the syringe.</u>

Warnings and precautions
Hepatotoxicity
Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported (see section Undesirable effects). ~~One fatal event of acute liver failure has occurred.~~ Liver enzymes (including ALT, AST and bilirubin) should be monitored prior to initiation of treatment with

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Tepmetko, then every two weeks during the first three months of treatment and then once monthly or as clinically indicated. in patients found to have elevated transaminases or bilirubin levels, more frequently tests should be performed. Depending on severity of adverse drug reactions, Tepmetko must be temporarily discontinued, the dose reduced or discontinued permanently (see section Dosage/Administration).

Undesirable effects

Summary of the safety profile

The safety profile of Tepmetko reflects exposure to tepotinib in 506 ~~448~~ patients with various solid tumours enrolled in five open-label, single-arm studies, in which patients received tepotinib as a single agent at a dose of 450 mg once daily. This includes 313 ~~255~~ patients with advanced NSCLC harbouring METex14 skipping alterations included in the main clinical study (VISION).

The most common adverse reactions observed in the main clinical study (VISION) were oedema (80.2% ~~69.0%~~ of patients), mainly peripheral oedema (72.5% ~~60.0%~~), nausea (31% ~~26.7%~~), diarrhoea (28.8% ~~26.3%~~), increase in creatinine (30.4% ~~25.9%~~), hypoalbuminaemia (33.9% ~~23.9%~~) and fatigue (15.7%). Most common serious adverse reactions were reported for generalised oedema (1.9% ~~2.0%~~) and peripheral oedema (3.2% ~~2.4%~~).

Peripheral oedema was the most frequent cause of permanent treatment discontinuation (5.4% ~~3.5%~~), temporary treatment discontinuation (19.8% ~~16.9%~~) or dose reduction (15.7% ~~14.1%~~).

Table 2: Adverse reactions in patients with solid tumours receiving the target dose

System organ class/Adverse reaction	**Tepmetko N=506 ~~448~~**			
	All grades		**Grade ≥ 3**	
	n (%)	**Frequency category**	**n (%)**	**Frequency category**
Metabolism and nutrition disorders				
Hypoalbuminaemia[a]	150 (29.6) ~~104 (23.2)~~	Very common	25 (4.9) ~~19 (4.2)~~	Common
Appetite decreased	116 (22.9) ~~89 (19.9)~~	Very common	10 (2.0) ~~7 (1.6)~~	Common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[b]	97 (19.2) ~~74 (16.5)~~	Very common	11 (2.2) ~~10~~	Common
Pleural effusion	60 (11.9) ~~48 (10.7)~~	Very common	14 (2.8) ~~(3.1)~~	Common
ILD/ILD-like reactions[c,*]	10 (2.0) ~~8 (1.8)~~	Common	1 (0.2)	Uncommon
Gastrointestinal disorders				
Diarrhoea	141 (27.9) ~~118 (26.3)~~	Very common	7 (1.4) ~~6 (1.3)~~	Common
Nausea	135 (26.7) ~~106 (23.7)~~	Very common	7 (1.4) ~~5 (1.1)~~	Common
Vomiting	73 (14.4) ~~61 (13.6)~~	Very common	7 (1.4) ~~(1.6)~~	Common
Increase in amylase[d]	44 (8.7) ~~30 (6.7)~~	Common	13 (2.6) ~~11 (2.5)~~	Common
Increase in lipase[e]	44 (8.7) ~~34 (7.6)~~	Common	23 (4.5) ~~21 (4.7)~~	Common
Hepatobiliary disorders				
Increase in alanine aminotransferase (ALT)	77 (15.2) ~~49 (10.9)~~	Very common	16 (3.2) ~~14 (3.1)~~	Common
Increase in alkaline phosphatase (ALP)	50 (9.9)	Common	5 (1.0)	Common

	~~35 (7.8)~~		~~4 (0.9)~~	~~Uncommon~~
Increase in aspartate aminotransferase (AST)	69 (13.6) ~~45 (10.0)~~	Very common	17 (3.4) ~~14 (3.1)~~	Common
Renal and urinary disorders				
Increase in creatinine[f]	123 (24.3) ~~93 (20.4)~~	Very common	7 (1.4) ~~4 (0.9)~~	Common ~~Uncommon~~
General disorders and administration site conditions				
Oedema[g]	357 (70.6) ~~281 (62.7)~~	Very common	52 (10.3) ~~30 (6.7)~~	Common
Fatigue	95 (18.8) ~~84~~	Very common	12 (2.4) ~~10 (2.2)~~	Common
Generalised oedema	29 (5.7) ~~21 (4.7)~~	Common	10 (2.0) ~~7 (1.6)~~	Common

* ILD as per Integrated Assessment

a includes terms hypoalbuminaemia, blood albumin decreased

b includes terms dyspnoea, dyspnoea at rest, exertional dyspnoea

c includes terms interstitial lung disease, pneumonitis, acute respiratory failure, lung fibrosis and radiation pneumonitis

d includes terms amylase increased, hyperamylasaemia

e includes terms lipase increased, hyperlipasaemia

f includes terms blood creatinine increased, hypercreatinaemia

g includes terms oedema peripheral, oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema

Description of selected adverse reactions

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) or ILD-like adverse reactions have been reported in 8 ~~6~~ patients (2.6% ~~2.4%~~) with advanced NSCLC with METex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (n=313 ~~255~~), including 1 case of grade 3 or higher; serious cases occurred in 4 ~~2~~ patients (1.3% ~~0.8%~~), 1 case was fatal (see sections Dosage/Administration and Warnings and precautions).

Hepatoxicity

Hepatotoxicity has occurred in patients treated with Tepmetko. In the main clinical study, an increase of at least 1 grade was observed for 49.5% of patients for ALT and 39.9% of patients for AST. An increase to grade 3 or higher occurred in 4.9% of patients for ALT and 3.6% of patients for AST ~~ALT/AST elevations occurred in 12.2% of patients. In 3.1% of patients, an increase in ALT/AST to grade 3 or higher was observed. In one patient, a fatal case of liver failure occurred.~~ No patients treated with Tepmetko discontinued treatment due to elevated ALT/AST. The median time to onset of an elevated ALT/AST increase to grade 3 or higher was 9.9 ~~7.3~~ weeks (time range 3.1 to 37.4 ~~8.6~~ weeks) (see sections Dosage/Administration and Warnings and precautions).

ALP increase did not lead to any dose reductions, temporary discontinuation, or permanent discontinuation. The observed ALP increase was not associated with cholestasis. Based on laboratory values, a worst-on-treatment increase of at least 1 grade was observed for 51.6% ~~47.5%~~ of patients for ALP in the main clinical study. An increase to grade 3 or higher occurred in 1.6% of patients.

Increase in creatinine

Based on laboratory values, shifts of at least 1 grade in creatinine were documented for 59.9% ~~52.9%~~ of patients in the main clinical study; three ~~one~~ patients had a shift to a grade 3 creatinine increase. A median increase in serum creatinine of 30% ~~31%~~ was observed 21 days after initiation of treatment with Tepmetko. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion (see section Warnings and precautions).

Increase in amylase or lipase
Increases in amylase or lipase were generally asymptomatic and not associated with pancreatitis and could be managed without dose reduction.
Based on laboratory values, - an increase of at least 1 grade was observed for 24.9% ~~21.6%~~ of patients for amylase and 21.2% ~~17.3%~~ of patients for lipase in the main clinical study. An increase to grade 3 or higher occurred in 5.3% ~~4.3%~~ of patients for amylase and 5.3% ~~3.5%~~ of patients for lipase.

QTc prolongation
In the main clinical study (patients with METex14 skipping alterations, n=313 ~~255~~); QTcF prolonged to > 500 ms was observed in 8 ~~6~~ patients (2.6% ~~2.4%~~) and QTcF prolonged by at least 60 ms from baseline in 19 ~~12~~ patients (6.1% ~~4.7%~~) (see section Warnings and precautions). The findings were isolated and asymptomatic, the clinical significance is unknown. In an exposure-response QTc analysis, no significant changes in the QTc interval (> 20 ms) were found on average at the therapeutic dose, but a concentration-dependent prolongation was found (see section Properties/Effects, Cardiac electrophysiology).

Clinical efficacy
The efficacy of tepotinib was evaluated in a single-arm, open-label, multicentre study (VISION) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring METex14 skipping alterations (n=313 ~~152~~). Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and were either treatment-naïve or had progressed on up to 2 lines prior systemic therapies. Neurologically stable patients with central nervous system metastases were permitted. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) activating alterations were excluded.

The primary efficacy outcome measure was confirmed objective response (complete response or partial response, ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included complete response, partial response, duration of response (DOR) and progression-free survival (PFS), assessed by IRC, as well as overall survival (OS).

Patients had a median age of 72 ~~73~~ years (range 41 to 94), 51% ~~48%~~ were female and 49% ~~52%~~ male. The majority of patients were white (62% ~~71%~~), followed by Asian patients (34% ~~25%~~) and were never (49% ~~43%~~) or former smokers (45% ~~50%~~). Most patients were ≥ 65 years of age (79% ~~82%~~) and 41% ~~45%~~ of patients were ≥ 75 years of age.

The majority of patients had stage IV disease (94% ~~98%~~), 81% ~~86%~~ had adenocarcinoma histology. Thirteen ~~Ten~~ percent of the patients had stable brain metastases. Patients received tepotinib as first-line (52% ~~45%~~) or second- or later line (48% ~~55%~~) therapy.

METex14 skipping alterations were prospectively tested by next-generation sequencing in tumour (RNA-based) and/or plasma (ctDNA-based).

Patients received 450 mg tepotinib once daily until disease progression or unacceptable toxicity. Median treatment duration was 7.5 ~~7.03~~ months (range 0 ~~0.03~~ to 72 ~~43.33~~ months).

In the initial efficacy analysis 152 adult patients with locally advanced or metastatic NSCLC harbouring METex14 skipping alterations with a follow up of at least 9 months were evaluated (see Table 3). ~~The primary efficacy outcome measure was confirmed objective response (complete~~

~~response or partial response) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included complete response, partial response, duration of response and progression-free survival assessed by IRC as well as overall survival.~~

In an extended efficacy analysis additional 161 adult patients with locally advanced or metastatic NSCLC harbouring METex14 skipping alterations were enrolled into the VISION study. Overall, efficacy results refer to 313 patients with a follow up of at least 18 months.

In the overall population of 313 patients, 161 patients showed either a partial (n = 160) or a complete (n = 1) response, resulting in an ORR of 51.4% (95%-CI 45.8, 57.1%). A median DOR of 18.0 months (95%-CI 12.4, 46.4 months) is observed, with 65.8%, 49.7%, and 38.5% out of 161 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 11.2 months (95%-CI 9.5, 13.8 months) and a median OS of 19.6 months (95%-CI 16.2, 22.9 months) was observed.

In 164 treatment naive patients, 94 patients showed either a partial (n = 93) or a complete (n = 1) response resulting in an ORR of 57.3% (95%-CI 49.4, 65.0%). A median DOR of 46.4 months (95%-CI 13.8, ne months) is observed, with 66.0%, 51.1%, and 40.4% out of 94 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 12.6 months (95%-CI 9.7, 17.7 months) and a median OS of 21.3 months (95%-CI 14.2, 25.9 months) was observed.

In 149 previously treated patients, 67 patients showed a partial response resulting in an ORR of 45.0% (95%-CI 36.8, 53.3%). A median DOR of 12.6 months (95%-CI 9.5, 18.5 months) is observed, with 65.7%, 47.8%, and 35.8% out of 67 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 11.0 months (95%-CI 8.2, 13.7 months) and a median OS of 19.3 months (95%-CI 15.6, 22.3 months) was observed.

השינויים בעלון לצרכן הינם (טקסט שנוסף מופיע עם קו תחתון, טקסט שנמחק מופיע עם ~~קו חוצה~~):

כיצד תשתמש בתרופה

[...]

צורת הנטילה

טפמטקו מיועד לנטילה דרך הפה.

יש לבלוע את הטבליות בשלמותן, מבלי ללעוס, יחד עם אוכל או זמן קצר לאחר הארוחה.

במידה ואתה מתקשה לבלוע את הטבליות, אתה יכול לערבב אותם במים

- שים את הטבליות בכוס
- הוסף 30 מ"ל מים (לא תוססים), אין להשתמש בכל נוזל אחר
- ערבב את המים עד שהטבליה מתפרקת לחתיכות קטנות מאוד, הטבליה לא תתמוסס לחלוטין
- שתה את הנוזל מיד, יחד עם אוכל
- כדי לוודא שנטלת את כל התרופה, מזוג 30 מ"ל נוספים של מים לכוס ושתה אותם

[...]

למידע המלא יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום מרק סרונו בע"מ, רח' הקישון 18, יבנה 81220, טל' 09-9510737.

בברכה,

אורית פוקס
רוקחת ממונה