Report TEPMETKO® tepotinib

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<tr><th>Product &
Mechanism of action</th><th>Authorized indications
Licensing status</th><th>Essential therapeutic features</th><th>NHS impact</th></tr>
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<td>
Substance: tepotinib

Brand Name: Tepmetko

Originator/licensee: Merck Europe B.V.

Classification: NCE

ATC code:L01EX21

OrphanStatus:
Eu:No
Us: Yes

Mechanism of action:
Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits HGF-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations [1].
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Authorized Indication:
EMA: Tepotinib as monotherapy is indicated for the treatment of adult pts with advanced NSCLC harbouring alterations leading to METex14 skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy[2].

FDA: tepotinib is indicated for the treatment of adult pts with metastaticNSCLC harboring MET exon 14 skipping alterations [1].

Route of administration: OS

Licensing status
EU CHMP P.O. date:16/12/2021
FDA M.A. date: 03/02/2021

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
AE: Adverse Events
CHMP: Committee for Medicinal Products for Human Use
CR: Complete Response
HGF: hepatocyte growth factor
M.A.: Marketing Authorization
MET:mesenchymalepithelial transition
METex14:mesenchymal-epithelial transition factor gene exon 14
NSCLC:non-small cell lung cancer
ORR: Objective Response Rate
P.O.: Positive Opinion
PR: Partial Response
Pts: patients
SAEs: Serious Adverse Events
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Summary of clinical EFFICACY:
VISON study (NCT 02864992) was an open-label, phase II study that aimed to assess the antitumor activity and side-effect profile of tepotinib 500 mg in adults (n=99) with advanced or metastatic NSCLC with a confirmed MET exon 14 skipping mutation. Enrolled subjects were administered tepotinib once daily in 21-day cycles until progression of disease, withdrawal of consent, AE leading to discontinuation, or death. Treatment was continuous with no interruption between cycles [3].
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<tr><th></th><th>Study protocol</th><th>Study results</th></tr>
<tr><td>Primary Endpoint</td><td>Confirmed ORR (defined as CR or PR) on the basis of an assessment by an independent review committee.</td><td>The ORR was 46% (95% CI, 36 to 57).
All the responses were PR, no pts had CR.</td></tr>
<tr><td>Secondary Endpoint</td><td>Investigator-assessed ORR</td><td>The ORR was 56% (95% CI, 45 to 66).
Two pts had a CR and 53 pts had a PR</td></tr>
<tr><td rowspan="2">Additional analysis</td><td rowspan="2">Detection of a MET exon 14 skipping mutation on liquid biopsy or tissue biopsy</td><td>- Independent review ORR: 48% (95% CI, 36 to 61) in the liquid-biopsy group and 50% (95% CI, 37 to 63) in the tissue-biopsy group.</td></tr>
<tr><td>- Investigator-assessed ORR: 56% (95% CI, 43 to 68) in the liquid-biopsy group and 62% (95% CI, 48 to 74) in the tissue-biopsy group.</td></tr>
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Summary of clinical SAFETY:
AEs of any cause were reported in 98% of pts during treatment. AEs that were considered by the investigators to be related to tepotinib were reported in 89% of pts. The most common of these AEs of grade three or higher was peripheral edema (in 7%). Increased levels of amylase and lipase were common but were of mild to moderate severity. SAEs that were considered to be related to tepotinib were reported in 15% of pts. A total of 21 pts had AEs leading to death while receiving tepotinib; one death of a patient with respiratory failure and dyspnea, secondary to interstitial lung disease, was considered by investigators to be related to tepotinib [3].

Ongoing studies:
● For the same indication: Yes
● For other indications: Yes

Discontinued studies (for the same indication): No

References:

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https://clinicaltrials.gov/ct2/home

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Cost of therapy:
The US cost for tepotinib oral tablet 225 mg is around $10,919 for a supply of 30 units [4].

Epidemiology:
In Europe, lung cancer is estimated to be the second most common cancer and the leading cause of cancer-related mortality, responsible for 388,000 deaths in 2018. NSCLC accounts for 80%-90% of lung cancers [5].Mutations in MET signaling pathways, including alterations causing METex14 skipping, occur in 3-4% of NSCLC cases and are associated with advanced disease and poor prognosis [6].

POSSIBLE PLACE IN THERAPY
There are currently no treatments approved to specifically target METex14 skipping mutation or c-MET gene amplification [7].
There are encouraging results from a study involving capmatinib+ gefitinib and gefitinib + tepotinib. Moreover, there are ongoing studies involving osimertinib and rocelitinib in combination with capmatinib and savolitinib [8].

OTHER INDICATIONS IN DEVELOPMENT: Yes (Colorectal Cancer, Hepatocellular Carcinoma) [9].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:No.

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Yes (Ningetinib, Capmatinib, Savolitinib, Cabozantinib) [9].
*Service reorganization Y/N: No
*Possible off label use Y/N: Yes

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