HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

23 JUNE 2021

The legally binding text is the original French opinion version

rifaximin

TIXTAR 550 mg film-coated tablets

TARGAXAN 550 mg film-coated tablets

Re-evaluation

Key points

Favourable opinion for reimbursement only in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors.

Unfavourable opinion for reimbursement in other situations.

What therapeutic improvement?

TIXTAR or TARGAXAN medicinal products containing rifaximin provide a therapeutic improvement in the management of this condition.

Role in the care pathway?

Management is based on the identification and correction of triggering factors (infection, gastrointestinal bleeding, excessive protein intake, kidney failure, dehydration, electrolyte disturbances, sedative medicinal products, gastrointestinal disorders such as constipation). For overt HE, the preventive treatment of encephalopathy is based primarily on the use of lactulose (DUPHALAC) or lactitol (IMPORTAL), orally or as an enema, aimed at reducing blood ammonia levels, or the implementation of a low-protein diet. When encephalopathy is severe (coma), hospitalisation in an intensive care unit and assisted ventilation may be necessary. Finally, liver transplantation may be necessary in the event of refractory and/or recurrent chronic hepatic encephalopathy but it can only be performed in a minority of patients.

Role of TIXTAR (rifaximin) or TARGAXAN (rifaximin)

Based on the available clinical data, rifaximin, primarily used in combination with lactulose, can be offered for the prevention of recurrence of episodes of breakthrough hepatic encephalopathy, in adult patients with at least two previous episodes of hepatic encephalopathy, only following elimination of triggering factors.

In other situations, to date, rifaximin has no role in the care pathway.

Special recommendations

The Committee recommends that prescription be limited to internal medicine specialists and hepato-gastroenterology specialists.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

TIXTAR (rifaximin)

Clinical benefit

◗ Hepatic encephalopathy is a serious complication of cirrhosis, characterised by neuropsychiatric manifestations. Symptomatic manifestations cover a broad spectrum, from minor disturbances of higher functions through to coma, which can be life-threatening.
◗ Rifaximin is a preventive treatment that has demonstrated its efficacy in combination with lactulose in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (i.e. with at least two previous episodes of hepatic encephalopathy and on condition that triggering factors have been eliminated).
◗ Its efficacy/adverse effects ratio remains high in these patients.
In the absence of available data and given that other forms of encephalopathy must be treated by management of triggering factors, the efficacy/adverse effects ratio is not established in these patients.
◗ In addition to TARGAXAN (rifaximin), there are therapeutic alternatives represented by lactulose (DUPHALAC) and lactitol (IMPORTAL).
◗ TIXTAR (rifaximin) is a first-line treatment in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (i.e. with at least two previous episodes of hepatic encephalopathy and on condition that triggering factors have been eliminated).
In other situations, TIXTAR (rifaximin) has no role in the care pathway.

Public health impact

Considering:

- the seriousness and prevalence of overt hepatic encephalopathy, with a risk of prolonged or repeated hospitalisations in the event of recurrent hepatic encephalopathy,
- the partially met medical need,
- the additional response to the identified need given the available data from pivotal studies and new data despite the reservations expressed (see section 08.6 **Erreur ! Source du renvoi introuvable.**~~Résumé & discussion~~):
    - demonstrating the efficacy of rifaximin in combination with lactulose versus placebo in terms of the risk of occurrence of a breakthrough overt HE episode at 6 months, with maintenance of efficacy after 2 years
    - demonstrating a reduction in mortality, despite methodological reservations,
    - suggesting an improvement in quality of life
- a potential additional impact on the organisation of care due to the reduction in hospitalisation risk,

TIXTAR (rifaximin) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of TIXTAR (rifaximin) remains substantial only in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors.
The clinical benefit remains insufficient to justify public funding cover in all other clinical situations.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other situations.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

- **In the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors:**

Considering:

- data from the pivotal studies already evaluated (RFHE3001 double-blind study and RFHE3002 open-label study) having demonstrated the efficacy of rifaximin 550 mg versus placebo in terms of the risk of occurrence of a breakthrough overt HE episode, in combination with lactulose, at 6 months, with maintenance of efficacy after 2 years
- new available data on morbidity and mortality derived primarily from the meta-analysis but including methodological reservations,
- the substantial medical need given the high risk of recurrence in patients who already have a history of two prior episodes of hepatic encephalopathy,

the Committee considers that TIXTAR (rifaximin) provides a minor clinical added value (CAV IV) in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (i.e. with at least two previous episodes of hepatic encephalopathy and following elimination of triggering factors).