HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
13 OCTOBER 2021

The legally binding text is the original French opinion version

setmelanotide
IMCIVREE 10 mg/ml solution for injection

Inclusion on list

Key points

Favourable opinion for reimbursement in the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Maintenance of this opinion is dependent on analysis of the results of ongoing studies on setmelanotide within a maximum period of one year.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The management of obesity is complex and requires a multidisciplinary approach combining dietary measures, physical activity and, if necessary, psychological support.

Beyond standard dietary measures and lifestyle changes, early onset obesity is difficult to treat. Conventional obesity treatments (behavioural approach, surgical or medicinal treatments, environmental changes) have poor efficacy and there is no treatment to manage hyperphagia.

Hence, bariatric surgery cannot address the underlying issue of the lack of a satiety signal in these patients and therefore cannot control the patient's hunger or obesity. The other potential surgical approaches, such as gastric or intestinal bypass operations, are considered to be contraindicated because such patients maintain an extreme appetite and overeat even after such surgical procedures, often leading to anatomical complications as a result.

In its guidelines, the HAS points out that bariatric surgery is not indicated in adolescents with severe and non-stabilised eating disorders, addictive behaviours or in patients with syndrome-related (for example, Prader-Willi syndrome), known monogenetic, or lesion-related obesity (apart from exceptions).

Endocrine therapies, particularly in patients with a POMC/PCSK1 deficiency, are often necessary (life-long glucocorticosteroid replacement therapy, treatment for any hypothyroidism).

There are currently no clinical guidelines for the treatment or management of obesity related to a POMC or LEPR deficiency.

Role of IMCIVREE (setmelanotide) in the therapeutic strategy:

Despite limited data from two non-comparative, open-label studies concerning a small number of patients, in the context of a very rare disease, the Committee considers that IMCIVREE (setmelanotide) is a first-line treatment for obesity and the control of hunger when it is associated with a biallelic pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin Type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

The adverse reactions reported for setmelanotide include generalised increased skin pigmentation and darkening of pre-existing nevi because of its pharmacologic effect. Full body skin examinations should be conducted annually to monitor pre-existing and new skin pigmentary lesions before and during treatment with setmelanotide.

In addition, in clinical trials, patients candidate for setmelanotide treatment were often depressed. Patients with depression should therefore be monitored at each medical visit during treatment with IMCIVREE (setmelanotide). Consideration should be given to discontinuing IMCIVREE (setmelanotide) if patients experience suicidal thoughts or behaviours.

Special recommendations

Considering:

- that obesity, even genetic, requires multidisciplinary management,
- current uncertainties with respect to the long-term safety of the product, particularly given the dermatological and psychiatric adverse events,

the Committee recommends that the decision to initiate setmelanotide treatment be taken at a multidisciplinary team (MDT) meeting and in reference centres. Particular attention must be paid to the dermatological and psychological follow-up of patients on setmelanotide.

In addition, the Committee would like to receive the results of ongoing studies on this medicinal product. It will re-evaluate IMCIVREE (setmelanotide) on the basis of the results of these studies and any other relevant data within a maximum period of 1 year.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Obesity and lack of control of hunger due to biallelic pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiency is a disease that can lead to very serious secondary consequences.

◗ The proprietary medicinal product IMCIVREE (setmelanotide) is a symptomatic medicinal product.

◗ The efficacy/adverse effects ratio of setmelanotide compared to placebo has not currently been adequately established. Additional data is required and expected to be able to determine, with a better level of evidence, the efficacy, effects and risks related to its use at the MA dosages and in the
MA indication.

◗ There are no therapeutic alternatives for the treatment of obesity and the control of hunger due to these specific genetic mutations.

◗ Despite limited data from two non-comparative, open-label studies concerning a small number of patients, in the context of a very rare disease, the Committee considers that IMCIVREE (setmelanotide) is a first-line treatment for obesity and the control of hunger when it is associated with biallelic pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin Type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.
Patients with depression should be monitored at each medical visit during treatment with IMCIVREE (setmelanotide). Consideration should be given to discontinuing IMCIVREE (setmelanotide) if patients experience suicidal thoughts or behaviours.

Public health impact

Considering:
- the seriousness of the disease in the long term and its very low prevalence,
- the unmet medical need,

but in view of:
- the lack of response to the identified need with, as knowledge currently stands, no demonstration of an impact on morbidity and mortality or quality of life due to a lack of data on these criteria in view of the data available only relative to weight reduction and satiety control, but also considering the safety profile (occurrence of nevi and depression, requiring appropriate monitoring),
- the lack of impact on the organisation of care in the absence of data,

IMCIVREE (setmelanotide) is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of IMCIVREE (setmelanotide) is substantial in the MA indications pending new data.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications and at the MA dosages.
Maintenance of this opinion is dependent on analysis of the results of ongoing studies on setmelanotide. The Committee will re-evaluate this medicinal product in the light of this data and any other relevant data within a maximum period of one year.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- data derived from the pivotal cohorts of two non-comparative open-label studies having demonstrated weight loss of at least 10% after one year of treatment in 8 out of 10 patients suffering from obesity and lack of hunger control with biallelic POMC, including PCSK1, deficiency and in 5 out of 11 patients with LEPR deficiency,
- variable results depending on the mutations but without the possibility of reaching a conclusion in the absence of a robust comparison,
- the absence of longer-term clinical data demonstrating, in particular, a reduction in the development of obesity complications,
- the absence of robust data relative to quality of life, which is particularly impaired,
- the occurrence of adverse events requiring specific monitoring (in particular cases of depression, including severe depression and the development of nevi),

the Transparency Committee considers that **IMCIVREE (setmelanotide) provides no clinical added value (CAV V) in the treatment of obesity and the control of hunger when it is associated with biallelic pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin Type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.**