SUMMARY

setmelanotide
IMCIVREE 10 mg/ml,
solution for injection
Reassessment

Adopted by the Transparency Committee on 15 February 2023

The legally binding text is the original French opinion version

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.

What therapeutic improvement?

Clinical added value in the therapeutic strategy on the basis of currently available data.

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 follow-up.

Beyond standard dietary measures and lifestyle changes, early onset obesity is difficult to treat. Conventional obesity treatments are sometimes insufficient (behavioural approach, surgical or medicinal treatments, environmental changes) 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 possible hypothyroidism).

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

Role of the medicinal product in the care pathway

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.

Setmelanotide can cause a generalised increase in 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 clinical trials, depression has been reported in patients treated with setmelanotide. However, this AE was not considered to be treatment-related. In accordance with the SmPC, patients with depression should therefore be monitored at each medical visit during treatment with IMCIVREE (setmelanotide) and consideration should be given to discontinuing IMCIVREE (setmelanotide) if patients experience suicidal thoughts or behaviours.

The new data submitted do not modify the role of IMCIVREE (setmelanotide) in the care pathway.

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.

Committee's conclusions

Clinical Benefit

- Obesity and lack of control of hunger due to biallelic pro-opiomelanocortin (POMC) and leptin receptor (LEPR) deficiency is a disease which can have 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 is high.
- There are no therapeutic alternatives for the treatment of obesity and the control of hunger due to these specific genetic mutations.
- Despite updating of the data from two non-comparative, open-label studies still concerning a very small number of patients, 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.

  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 benefit**

Considering:

- the seriousness of the disease in the long term and its very low prevalence,
- the partially met medical need,
- the partial response to the identified need, with an expected additional impact of IMCIVREE (setmelanotide) on morbidity due to weight loss and an improvement of satiety, but without a demonstrated impact on quality of life,
- the lack of additional impact demonstrated on the care and life pathway,

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

Considering all these elements, the Committee deems that the clinical benefit of IMCIVREE (setmelanotide) is substantial in the MA indication 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 MA indication and at the MA dosages.

Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- the points raised in the Committee's assessment in its opinion of 13 October 2021, in particular the variable results depending on the mutations, the absence of robust efficacy and quality of life data given the non-comparative methodology of the clinical studies, having included small numbers of patients, as well as the atypical safety profile of setmelanotide requiring increased monitoring, with, notably, cases of hyperpigmentation, depression and injection site reactions, and the limited experience in terms of long-term safety,
- updated data concerning a higher number of patients, but which nevertheless remains modest, with 10 to 14 patients analysed in the RM-493-012 study and 11 to 15 patients in the RM-493-015 study,
- the results appear to confirm those observed in the first assessment, with, in the RM-493-012 study, 85.7% of patients in the total cohort having achieved an at least 10% reduction in weight at 52 weeks compared to baseline, versus 80% of patients in the pivotal cohort; and in the RM-493-015 study, 53.3% of patients in the total cohort having achieved an at least 10% reduction in weight at 52 weeks compared to baseline, versus 45.5% of patients in the pivotal cohort,
- the suggested improvement in satiety, assessed as a secondary endpoint, in two non-comparative studies,
- the expected beneficial impact of weight loss and improvement of satiety in this condition characterised by morbid obesity (BMI greater than 40) at a very early age, often in young childhood,
- the partially met medical need in this rare, serious and disabling disease,

but despite:

- the absence of robust quality of life data, which is regrettable for this disease with a significant impact on the quality of life of patients and their caregivers,

the Transparency Committee considers that IMCIVREE (setmelanotide) provides a minor clinical added value (CAV IV) in the treatment of obesity and the control of hunger 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.