HAUTE AUTORITÉ DE SANTÉ

INTENSIVE CARE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

REVERPLEG (argipressin), vasopressin antagonist

Insufficient clinical benefit to justify its reimbursement in the treatment of hypotension refractory to catecholamines following septic shock

Main points

- REVERPLEG has been granted a marketing authorisation in the treatment of hypotension refractory to catecholamines following septic shock in patients over the age of 18 years.
- Its haemodynamic efficacy in maintaining mean arterial (MAP) pressure has been demonstrated, with a reduction of noradrenaline doses, in patients with already stabilised septic shock (off-label). No data offering a good level of evidence, demonstrating its efficacy in terms of reducing morbidity and mortality in patients suffering from hypotension induced by catecholamine-resistant septic shock, are available.
- Its impact on morbidity and mortality has not been demonstrated.
- The clinical benefit of reducing noradrenaline doses by adding another vasopressor, with no additional demonstrated benefit in terms of efficacy and/or safety, has not been established.
- Uncertainties remain concerning the dosages of REVERPLEG under actual conditions of use in cases of septic shock and on the associated risk of toxicity.

Therapeutic strategy

- The management of sepsis and septic shock in adults relies on various measures that must be implemented as early as possible: intravenous antimicrobial/antiviral treatment and control of the source of infection, haemodynamic support (vascular filling, vasopressors, dobutamine), along with other support therapies (such as glycaemic control, mechanical ventilation, renal dialysis, sedation and thromboprophylaxis).
- The first-line haemodynamic management of septic shock is based on early vascular filling (intravenous crystalloids within 3 hours) and subsequent volemic filling. Their aim is to restore sufficient arterial pressure (target MAP ≥ 65 mmHg) and to ensure adequate organ perfusion.
  Appropriate vasoactive treatment should be initiated in the event of hypotension refractory to vascular filling in order to maintain a MAP ≥ 65 mmHg at the onset of septic shock resuscitation. Noradrenaline is the recommended first-line vasopressor for the management of septic shock. If hypotension persists, low-dose vasopressin (up to 0.03 U/min.), or adrenaline may be considered in combination with noradrenaline to increase the MAP to the target value (second line). Vasopressin can be added to noradrenaline (second line) in order to reduce the doses of noradrenaline. Dopamine is recommended in the first line instead of noradrenaline, exclusively in closely selected patients, such as those presenting with bradycardia or at low risk of tachyarrhythmia, due to its increased risk of arrhythmia. Dobutamine may be used in the event of sepsis-induced myocardial failure in patients presenting signs of persistent hypoperfusion under vasopressors. Weaning off vasopressors should be performed as soon as haemodynamic stabilisation is achieved.
- To date, there is no consensus concerning the definition of a state of refractory septic shock. The REVERPLEG marketing authorisation defines hypotension refractory to catecholamines as " a mean arterial pressure that cannot be stabilised at a target value, despite adequate vascular filling and catecholamine treatment". Nevertheless, no details are available concerning the threshold dose of catecholamines, or time from which it is deemed appropriate to define patients as being in refractory shock and to administer vasopressin.
- **Role of the medicinal product in the therapeutic strategy**

The role of REVERPLEG in the treatment of hypotension refractory to catecholamines following septic shock cannot be established. Early antibiotic therapy, combined with optimum early haemodynamic management, remains the most effective treatment for septic shock and its complications.

Clinical data

- The assessment of REVERPLEG relies primarily on 2 randomised double-blind studies that assessed the effect of vasopressin in addition to catecholamines compared to noradrenaline.
- In the first study, 779 patients presenting with septic shock resistant to vascular filling and to low doses of noradrenaline (dose ≥ 5 µg/min.) were randomised to receive either a low dose of vasopressin (0.01 to 0.03 U/min.) combined with an initial perfusion of adrenaline, or noradrenaline alone (5 to 15 µg/min.). Upon inclusion, the MAP was of approximately 73 mmHg, serum lactate was of 3.5 mmol/L and the mean dose of noradrenaline was of 0.27 µg/kg/min. The mean time to perfusion of the test medicinal product was of approximately 12 hours. No statistically significant difference was observed between the two treatment groups in terms of mortality, whatever the cause, at 28 days (primary endpoint), nor any suggested difference between the two groups in terms of mortality, whatever the cause, at 90 days (exploratory secondary endpoint).
- In the second study, 24 patients in severe septic shock and pre-treated with high-dose catecholamines, were randomised to receive either vasopressin (0.01 to 0.08 U/min.), or noradrenaline (2 to 16 µg/min.) for 4 hours, in addition to the vasopressors openly administered. The median doses of noradrenaline and dopamine upon inclusion were respectively of 20.0 µg/min. and 2.5 µg/kg/min. in the noradrenaline group and of 25.0 µg/min. and 2.7 µg/kg/min. in the vasopressin group. The median MAP upon inclusion was of approximately 69 mmHg. After 4 hours of treatment, the addition of vasopressin helped reduce the associated initial doses of noradrenaline (-19.7 µg/min. compared to -3 µg/min. in the noradrenaline alone group), while maintaining the values of haemodynamic variables (exploratory endpoint). The median perfusion of vasopressin was of 0.06 U/min. (dosage not recommended). No variation was suggested between inclusion and 4 hours post-infusion in terms of variables reflecting the perfusion of target organs in the two treatment groups, with the exception of median urine output, that increased under vasopressin (+32.5 ml/h at 4 hours) (exploratory endpoints).
- In the first study, the incidence of serious adverse events was comparable in the vasopressin group (10.3%) and in the noradrenaline group (10.5%). Cases of digital ischaemia were more frequently reported under vasopressin than under noradrenaline (2% versus 0.5%). Conversely, cases of cardiac arrest (0.8% versus 2.1%) and acute mesenteric ischaemia (2.3% versus 3.4%) were less frequent under vasopressin.
- The efficacy of vasopressin, when used at the recommended dosages (0.01 to 0.03 U/min.) and in addition to catecholamines, was demonstrated in terms of reduction of initial noradrenaline doses, with maintenance of target MAP, in patients pre-treated with catecholamines for septic shock. The addition of low-dose vasopressin to noradrenaline failed to demonstrate any further advantage in terms of safety over noradrenaline alone. In both studies, vasopressin was administered in combination with catecholamines, whether or not the patients suffered from hypotension refractory to catecholamines (MAP on inclusion already in the recommended range ≥ 65 mmHg); no clinical data are available for the assessment of REVERPLEG in the treatment of sepsis-induced arterial hypotension refractory to catecholamines (marketing authorisation population).
- To date, there is no consensus concerning the definition of a state of refractory septic shock. No details are available concerning the threshold dose of catecholamines, or time from which it is deemed appropriate to define patients as being in refractory shock and to administer vasopressin.

Special prescription requirement

- Medicinal product for hospital use only, and in emergency situations.

Benefit of the medicinal product

- The actual clinical benefit* of REVERPLEG is insufficient.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 February 2019 (CT- 17185) available at **www.has-sante.fr**