HAUTE AUTORITÉ DE SANTÉ

PAIN
Update
February 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

SKUDEXUM (dexketoprofen/tramadol), fixed NSAID-weak opioid combination

Substantial actual clinical benefit in symptomatic short-term treatment of moderate to severe acute pain but no proven clinical added value compared to the current therapeutic strategy

Main points

- SKUDEXUM has Marketing Authorisation in the symptomatic short-term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen.
- Its superiority over the fixed paracetamol + tramadol combination has been demonstrated on the pain relief score over 6 hours post-treatment administration ($TOTPAR_6$), but the effectiveness was modest and of debatable clinical relevance.
- Concerns remain in respect of the safety of this fixed combination stemming from its ingredients (known adverse effects of tramadol and dexketoprofen) and in respect of the requirements for its prescription and use in routine practice.

Therapeutic strategy

- The management of acute pain must be adapted to the intensity and mechanism of the pain (inflammatory nociceptive, mechanical nociceptive, neuropathic or mixed).
- In cases of post-traumatic, postoperative, rheumatological and gynaecological acute nociceptive pain, optimally-dosed paracetamol is recommended for minor to moderate pain; a short course of NSAID therapy (in the absence of contraindications) or a weak opioid for moderate to intense pain and a weak or strong opioid for very intense pain, based on the urgency of the required pain relief and the clinical context.
  In cases of acute dental pain, it is recommended to prescribe, as a first-line treatment, paracetamol for low-intensity pain and an NSAID or a weak opioid (tramadol ± paracetamol, codeine + paracetamol) for moderate to intense pain.
- **Role of the medicinal product in the therapeutic strategy**

  Subject to compliance with its prescription requirements (particularly the period of use limited to 5 days) and with its numerous contraindications and precautions for use associated with the presence of dexketoprofen and tramadol, SKUDEXUM is a second-line medicinal product in the symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen.

Clinical data

- During the initial application assessment of SKUDEXUM (June 2016), two randomised double-blind studies compared SKUDEXUM administered as a single and repeated dose every 8 hours for 3 or 5 days with each of its components as a monotherapy (dexketoprofen 25 mg or tramadol 100 mg), in 1,247 patients after abdominal hysterectomy (n=606) or hip arthroplasty (n=641). The superiority of SKUDEXUM over the components alone at the same dose for dexketoprofen (25 mg) and at a higher dose for tramadol (100 mg) was demonstrated bymean SPID8 at rest (primary endpoint), defined by the weighted sum of the pain intensity score difference at rest calculated over 8 hours after the first administration using a 100 mm visual analogue scale (VAS).

- A randomised, double-blind non-inferiority study, including a superiority analysis, compared the fixed dexketoprofen 25 mg / tramadol 75 mg combination to the fixed paracetamol 650 mg / tramadol 75 mg combination, administered as a single dose, in 653 patients with acute pain of moderate to severe intensity (score ≥ 4 on the 11-point NRS numeric scale) within 4 hours following lower 3rd molar extraction. The superiority of SKUDEXUM over the fixed paracetamol 650 mg / tramadol 75 mg combination was demonstrated on $TOTPAR_6$, assessed using the 5-point VRS verbal scale (primary endpoint): 13 points versus 9 points, with a difference of 3.95 points (95% CI [2.69 ; 5.20]; p<0.0001).
- Although superiority was demonstrated over the fixed paracetamol 650 mg / tramadol 75 mg combination, considered as one of its clinically relevant comparators, the clinical relevance of the difference observed in terms of $TOTPAR_6$ (4 points) is difficult to interpret failing a clearly defined clinical relevance threshold for this score, contrary to the VAS.
- No new adverse events compared to those previously identified with this proprietary medicinal product were observed. The most frequent adverse events were vomiting, nausea, vertigo and drowsiness.

Benefit of the medicinal product

- The actual clinical benefit* of SKUDEXUM is substantial in the symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen.
- SKUDEXUM does not provide clinical added value** (CAV V) in the therapeutic short-term treatment strategy for acute pain of moderate to severe intensity.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was drafted on the basis of the Transparency Committee opinion dated 7 February 2018 (CT-16439) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”