FERGUS COUTTS
VETERINARY PAIN MANAGEMENT

Broadleys Veterinary Hospital
Stirling
FK7 7LE
Appointments: 01786 445665

Pharmacology of pain: Galliprant ™

Key points:

1. Grapiprant is a prostaglandin receptor antagonist, in the 'piprant' class of drugs.
2. Galliprant is the first in this class to be marketed for clinical use (due UK in early 2019).
3. Galliprant is regarded as an atypical NSAID, antagonising one PGE-2 receptor.
4. By targeting pain galliprant allows other PGs to exert their physiological functions in:
    - The kidney – maintaining renal blood supply.
    - GI tract - maintaining GI tract health by increasing production of mucus and $HCO3^-$.
    - Heart disease - maintaining ion balance in the kidney.

Grapiprant (Galliprant™) is a 'piprant', a novel drug class of prostaglandin receptor antagonists, approved for treating OA-related pain and inflammation in dogs and likely to be released in the UK during 2019.

1. Background

- Vane [8-10] discovered COX-1 and COX-2 isoenzymes both produce a common precursor PGH-2, from which tissue-specific enzymes produce prostaglandins (with homeostatic & pathological functions (fever, inflammation and pain).
- Prostaglandin E-2 (PGE2) is associated with nociception and peripheral sensitisation.
- PGD2, PGE2, PGF2 & PGI2 also have physiological functions, including maintenance of renal glomerular perfusion and GI mucosal integrity [10].
- NSAIDs reduce pain and inflammation by inhibiting COX-1 & COX-2 and reducing production of PGE2.
- NSAIDs may also have adverse effects on the physiology of electrolyte balance and function of GI tract & kidney.

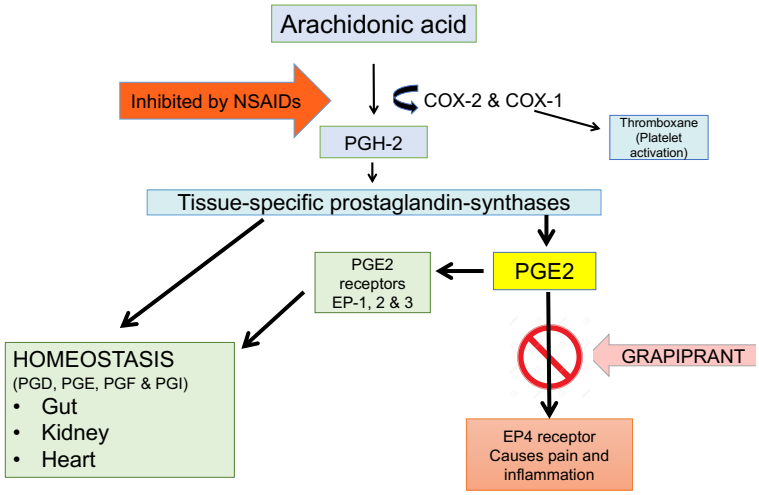
2. Safety & efficacy of grapiprant

- **Long-term safety:** Grapiprant was administered to dogs at up to 15 times the recommended therapeutic dose and for 9 months, with no adverse effects [5].
- **Efficacy:** 'Caregiver-placebo' is a factor known to confound studies into the efficacy of drugs to treat OA. Rausch-Derra et al (2016) conducted a prospective, randomized, masked, placebo-controlled study study, where vets and owners were blinded to which product was being administered. The results indicated that the EP4 receptor antagonist drug grapiprant showed effectiveness comparable to COX-inhibiting NSAIDS [4].

3. How Galliprant works (See Figure 1).

- The effects of PGE-2 are mediated by at least four receptors, designated EP1, EP2, EP3 and EP4.
- The range of biological functions and secondary messenger mechanisms of the PGE2 EPs are reviewed in detail by Woodward et al (2011) [11].
- The discovery of PG receptor antagonists led to the development of grapiprant, a proven EP4-antagonist [7]

Figure 1: Grapiprant targets pain and inflammation, preserving physiological function of PGs.



4. Clinical summary

- Grapiprant provides several clinical benefits in the management of OA-related pain.
  - Targeting the PGE2 receptor EP4, preserving homeostatic effects of PGE2 and other prostaglandins.
  - Offers pain relief to dogs from whom NSAIDs are contraindicated due to comorbidities, or withdrawn following renal or GI adverse effects.
  - PGE-2 receptors EP1-EP4 have overlapping function suggest grapiprant may be safer, but not a 'silver bullet'.
- Bradbrook and Clark (2018), p79, noted analgesic efficacy has not been demonstrated for acute pain in dogs and concluded "*The use of grapiprant in the acute pain setting [for dogs] cannot therefore be currently recommended* [2].
- The safety [6] and pharmacokinetics [3] of grapiprant has been reported in cats, with no renal or GI adverse effects noted. However, Adrian et al (2018) noted further studies demonstrating pain-relieving efficacy in cats are required before grapiprant is used in feline practice [1].

References available on request ***Jan 2019 (Rev. Mar 2021)***