BUDDLE FINDLAY

29 April 2022

To
Anthony Stewart
Senior Investigator
Commerce Commission
44, The Terrace
Wellington 6140
New Zealand

From
Laura Green
Tony Dellow

By Email
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Dear Anthony

Zoetis/Jurox: Market definitions of pre-anaesthetics and sedatives for companion animals

1. We refer to the Statement of Unresolved Issues (**SOUI**) released on 9 March 2022 in relation to the proposed acquisition of Jurox by Zoetis. The SOUI provided that the Commission is yet to reach a final view on the market definitions and invited submissions on its proposed definitions.

2. Zoetis has considered the Commission's proposed market definition of a butorphanol-based pre-anaesthetics and sedatives for companion animals market (the **butorphanol sedative market**), and the Commission's reasons for that proposed definition. In this submission, Zoetis argues that opioid-based pre-anaesthetics and sedatives is a more accurate market definition. The reasons for that are:

   (a) butorphanol-based sedatives have both sedative and analgesic uses, based on the ACVM indications of the products; and

   (b) the butorphanol-based sedatives are close substitutes with other opioid-based pre-anaesthetic and sedative products, as demonstrated by:

      (i) overseas anaesthesia guidance;

      (ii) the small quantities of butorphanol-based products sold in New Zealand, meaning they can be, and are, substituted with other opioid-based products on a routine basis; and

      (iii) acceptance of their substitution by the ACCC.

3. We provide further information about each of those reasons below and include a table in Appendix 1 setting out Zoetis' submissions on specific paragraphs of the SOUI.

Indications and usages

4. There is a contradiction in the SOUI's approach to the indications and usages of the products. At paragraph 40, the SOUI distinguishes between opioids and non-opioids on the basis that opioids have analgesic effects, whereas non-opioids do not. However, at paragraph 43.1, the SOUI states

"buprenorphine primarily acts as an analgesic, providing pain relief, while butorphanol primarily acts as a sedative". Butorphanol-based pre-anaesthetics and sedatives are opioids, and have analgesic effects in addition to sedation.

5. The SOUI places insufficient weight on the ACVM registered labels, which indicate that butorphanol products have both analgesic and sedative uses.

6. Torbugesic's ACVM-approved details are:

Details

Registration number **A007730**
Trade name **TORBUGESIC**
Registrant name **Zoetis New Zealand Limited**
Status **ACVM Registered**
Registrant address **Level 4, 8 Mahuhu Crescent,, AUCKLAND 1010, New Zealand**
Registration date **25-11-1999**

Product Types

Sedative
Analgesic

Conditions

[show details]
60, 61, 62, 63, 64, 65, 66, 67, 69, 70, 71, 72, 73,

Active Ingredients

Ingredient	Content	Unit
butorphanol tartrate	10	g/litre

Butordyne's ACVM approved details are:

Registration details

Details

Registration number **A010981**
Trade name **Butordyne Injection**
Registrant name **Jurox New Zealand Ltd**
Status **ACVM Registered**
Registrant address **8 Kordel Place, East Tamaki, AUCKLAND 2013, New Zealand**
Registration date **24-09-2013**

Product Types

Analgesic
Sedative

Conditions

[show details]
60, 61, 62, 63, 64, 65, 66, 67, 69, 70, 71, 72, 73,

Active Ingredients

Ingredient	Content	Unit
butorphanol tartrate	10	g/litre

7. Irrespective of anecdotal evidence that the Commerce Commission may have collected in its market investigations, the ACVM is the decision-maker in relation to the registration of veterinary medicines and their label claims, under the Agricultural Compounds and Veterinary Medicines Act 1997. The registrant of the originator product has provided clinical trial and other data to establish the validity of its claims for the purposes of ACVM registration, and the ACVM is satisfied that the data is sufficient to support analgesic and sedative indications for Torbugesic and Butordyne.

8. At paragraph 26, the SOUI gives weight to the ACVM recommendation that veterinarians should follow the 'on-label' indications of each animal health care product. Zoetis submits that the Commission should similarly respect the 'on-label' indications of the ACVM register in relation to the indications of butorphanol-based pre-anaesthetics and sedatives.

9. [ ].

Substitutable products

Sedatives in general terms

10. Zoetis agrees with the general statement at paragraph 34 of the SOUI that sedatives are either used as:

    (a) **pre-anaesthetic sedation**: to calm an animal prior to it being administered with an anaesthetic; or

    (b) **examination sedation**: to restrain an animal prior to a clinical exam or minor procedure.

11. The market analysis in the SOUI focuses on the pain relief attributes of butorphanol and other opioids. Pain relief properties are relevant to pre-anaesthetic sedation, as discussed in detail below, and can also be relevant to examination sedation, particularly where minor but still painful procedures are being undertaken.

12. In practice, it would be very rare for an opioid to be used by itself for sedation purposes only. Zoetis accepts this does occur very rarely, in cases where only light sedation is required (for example, for a cat requiring diagnostic radiographs that has significant respiratory issues). In practice, opioids are more commonly used as part of a drug combination, to:

    - enhance the sedative effects of the non-opioids, allowing lower doses to be used (ie, synergistic effects or additive effects that increase the level of sedation as well as the level of analgesia provided by the drugs);
    - provide pain relief during and immediately after the procedure; and
    - use balanced anaesthesia, where drugs are used in combination at the different phases of anaesthesia to improve the safety and comfort of the patient.

13. This is reflected in Troy's submission to the Commerce Commission. In section 4 of that submission Troy states "the products in Table 2 are generally not used or purchased in isolation of one another. This is largely because in carrying out procedures on companion animals a combination of drugs is used at the same time in order to achieve the correct level of sedation and pain control for the relevant procedure".

Range of considerations for veterinarians

14. Clinical decision-making about the products used in medical procedures requiring sedation and anaesthesia is complex. It is not a case of selecting a sedative and subsequently selecting an anaesthetic. The clinician selects products in combination with one another to achieve the desired effect, based on a number of considerations (see point 15 below). Butorphanol is just one opioid that can be used for sedation and frequently, like all other opioids, it is used in combination with a non-opioid anaesthetic for potentiation (the synergistic effect of mixing an opioid with a non-opioid sedative or anaesthetic).

15. As a starting point, Zoetis sets out the following factors and considerations that form the foundations of decision-making in relation to sedation and anaesthesia:

    (a) sedation and general anaesthesia are on a spectrum: a product or combination of products can sedate at a low dose and act as a general anaesthetic at a higher dose;

    (b) products are rarely used in isolation from one another, as procedures necessarily involve a combination of products (importantly, potentiation occurs with any opioid, and there is nothing unique about butorphanol in this respect);

    (c) different combinations of products offer different pros and cons and different safety margins;

    (d) anaesthetic sparing (dose reduction of induction and maintenance drugs, which have dose dependent adverse effects) is an important consideration for veterinarians;

    (e) a veterinarian will frequently schedule multiple surgeries on the same day;

    (f) a veterinarian will consider the patient, including the patient's starting health and any pre-existing conditions, as well as how easily the veterinarian can handle the patient both before and after the procedure;

    (g) a veterinarian will consider how long or short a time is needed for the recovery, as well as the smoothness of the recovery; and

    (h) a veterinarian will consider the procedure itself, including the length and the pain associated with the procedure as well as the likely duration of the pain. Different procedures call for different levels of sedation and anaesthesia. For example, a procedure in which a feral cat may require a (non-painful) clinical examination would require a different sedation from a procedure to lance and drain a cat bite abscess. For the former procedure, sedation is the desired effect, so medetomidine/buprenorphine may be appropriate, whereas the second procedure will require sedation in addition to a significantly greater degree of analgesia and a clinician may choose medetomidine, butorphanol, and ketamine or acepromazine/buprenorphine followed by alfaxalone.

16. A clinician will approach surgery with these principles and considerations in mind. While animal safety is the paramount concern, when planning an anaesthetic or sedative procedure, the cost of the procedure, and the affordability for the owner, are also important factors. Such factors may be relevant to the choice of pre-anaesthetic sedative and anaesthetic agent.

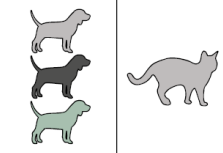
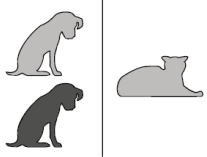
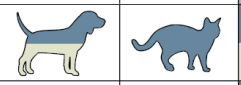
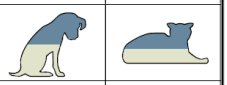
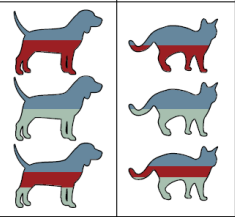
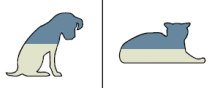
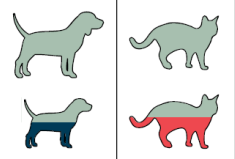
17. For completeness, Zoetis adds that many of the opioid sedatives are economical to use. If they are also safe and effective, this may make them an attractive choice for use in large patients that require larger volumes of drugs. The ability to manage the cost of a procedure requiring an anaesthetic or sedative may be the difference between an animal getting the procedure or not.

Evidence of the range of options for veterinarians

18. Varying levels of sedation are needed, depending on the procedure being undertaken or the outcome required. Clinicians have a wide range of options to achieve the right level.

19. The New Zealand Veterinary Association has not released anaesthesia guidelines, as is often the case in New Zealand for areas of specialised medicine. The guidelines released by the American Animal Hospital Association (**AAHA**) and American Association of Feline Practitioners (**AAFP**) demonstrate that different levels of sedation are required, and that there are numerous options and combinations available to a clinician to appropriately sedate an animal.

Table 1: AAHA Anaesthesia and Monitoring Guidelines for Dogs and Cats

Desired Effect	Drug Options	Healthy	Examples	Compromised/Sick
Low FAS	Gabapentin		50–150 mg/cat PO, 20–40 mg/kg PO (dog) 2–3 hr before visit	
	Trazodone		3–7.5 mg/kg PO (dog)	
	Alpha-2 agonist		Dexmedetomidine gel OTM. Use label dose for patient size**	
Light sedation	Opioid		Butorphanol 0.2–0.4 mg/kg IV/IM	
	Benzodiazepine		Midazolam 0.2 mg/kg, IV/IM	
Moderate sedation	Opioid		Butorphanol 0.4 mg/kg IM or Buprenorphine 0.02 mg/kg OTM (cat)	
	Tranquilizer		Acepromazine 0.01–0.03 mg/kg IM (dog)*, 0.025–0.1 mg/kg IM (cat)†	
	Benzodiazepine		Midazolam 0.2 mg/kg, IV/IM	
	Alpha-2 agonist		Dexmedetomidine 3–7 µg/kg IM (dog) or 3-10 µg/kg IM (cat) or 0.04 mg/kg OTM (cats)	
Heavy sedation	Opioid		Butorphanol 0.2–0.4 mg/kg IM	
	Benzodiazepine		Midazolam 0.2 mg/kg, IV/IM	
	Alpha-2 agonist		Dexmedetomidine 7–15 µg/kg IM (dog) or 10–20 µg/kg IM (cat)	
	Neurosteroid		Alfaxalone 1–2 mg IM§	
	Dissociative		Ketamine 1–2 mg/kg IM	

How to use this chart:

1. Select desired level of sedation.
2. Consider the combinations available.
3. Evaluate the health status of your canine or feline patient.
4. Taking into consideration patient demeanor, the anticipated length of, and degree of pain caused by the procedure, and other factors, select a color combination that suits you and your patient's needs.
5. Make appropriate combination choices, remembering to use the lower end of the drug dose when combining with other sedatives.

FAS, fear, anxiety, stress; OTM, oral transmucosal administration

* Maximum 2-3 mg total dose

† Maximum 1 mg total dose

§ Best used in small patients

** Administer to fractious patients in parking lot

20. Table 1 shows the various levels of sedation that are required. It also highlights that achieving these various levels usually requires combinations of drugs, both opioid and non-opioid. The table shows that buprenorphine can be used instead of butorphanol to achieve moderate sedation.

Further evidence for the well-established use of buprenorphine in this way is documented in peer reviewed publications such as Grint *et al.* 2010; Hunt *et al.* 2013; and Warne *et al.* 2014).[1]

Table 2: AAFP feline anaesthesia guidelines

Table 8 Opioids used for premedication

Drug	Dose	Route(s)	Comments
Buprenorphine	0.01–0.02 mg/kg	IM, IV	May antagonize the effects of other mu-opioid agonists Longer duration of action (4–6 h)
Butorphanol	0.1–0.4 mg/kg	IM, IV	May antagonize the effects of other mu-opioid agonists Moderate to good sedation, short duration (60–90 mins)
Meperidine	2–5 mg/kg	IM	Short duration (60–90 mins) with minimal sedation *Not to be given IV*
Fentanyl	2–5 µg/kg	IV	Short duration with minimal sedation
Hydromorphone	0.02–0.1 mg/kg	IM, IV	Moderate sedation with duration of 2–4 h
Methadone	0.2–0.5 mg/kg	IM, IV	Moderate sedation with duration of 2–4 h
Morphine	0.1–0.3 mg/kg	IM, IV	Moderate sedation with duration of 2–4 h
Oxymorphone*	0.02–0.1 mg/kg	IM, IV	Moderate sedation with duration of 2–4 h

21. Table 2 further demonstrates that clinicians can select an opioid for a particular situation, and that there is variation between all opioid-based products in terms of the duration and degree of sedation. Although not all of the opioids listed in Table 2 are available in New Zealand, butorphanol, buprenorphine, morphine, and methodone are available.

[1] Grint NJ, Alderson B, Dugdale AH, 'A comparison of acepromazine-buprenorphine and medetomidine-buprenorphine for preanesthetic medication of dogs' *J Am Vet Med Assoc* 237, 1431-7, 2010, Hunt JR, Grint NJ, Taylor PM, Murrell JC, 'Sedative and analgesic effects of buprenorphine, combined with either acepromazine or dexmedetomidine, for premedication prior to elective surgery in cats and dogs' *Vet Anaesth Analg* 40, 297-307, 2013, and Warne L, Bauquier S, Pengelly J, Neck D, Swinney G, 'STANDARDS OF CARE Anaesthesia guidelines for dogs and cats' *Australian Veterinary Journal* 96, 413-27, 2018.

Table 3: AAFP feline anaesthesia guidelines

Combination examples‡				
Opioid + dexmedetomidine	0.0025–0.005	IM, IV		61
Opioid + alfaxalone	2–3	IM, IV		
Opioid + dexmedetomidine + ketamine	0.0025–0.005 2–3	IM, IV	If the opioid and the dexmedetomidine are reversed there will be minimal residual effect with the low dose of ketamine	62
Opioid + acepromazine	0.05–0.1	IM, IV		
Opioid + dexmedetomidine + midazolam	0.0025–0.005 0.05–0.2	IM, IV	Each of these drugs is reversible if it is necessary to remove the sedative effects	63
Opioid + dexmedetomidine + alfaxalone	0.0025–0.005 1–2	IM, IV	The high end of the dose range may anesthetize the cat	64
Alfaxalone + dexmedetomidine	1–2 0.0025–0.005	IM, IV		

22. Table 3 shows different combinations for anaesthesia of cats where various opioids can be used depending on the degree of the opioid properties required. Table 3 does not distinguish between butorphanol-based opioids and other opioid-based products.

23. Drawing on Table 3, an example of a clinical situation in which opioids could be interchanged would be for a desired outcome of moderate sedation, where acepromazine and an opioid is used. In this case, morphine, butorphanol, or buprenorphine could be used. Both morphine and butorphanol have moderate sedative effects, which would add to the sedative effects of the acepromazine. Morphine would have a slightly longer duration of effect. Buprenorphine has less sedative effect but would give a much longer duration of pain relief which would be an advantage with longer more painful procedures.

24. The statement in the SOUI that butorphanol is an opioid that is unlikely to have a close substitute for sedation purposes is inconsistent with the above guidelines. Although it does have a different duration of action, level of analgesia and degree of sedation, other opioids can provide suitable, and often superior, sedation for companion animals.

[ ]

25. [ ].

26. [ ].

Approach of the ACCC

27. Zoetis acknowledges that the market definitions in New Zealand will not always be consistent with those overseas, but the approach taken to the definition of these markets by overseas regulators remains relevant. In its Statement of Issues about the proposed acquisition of Jurox by Zoetis, the ACCC defines the relevant market as the supply of pre-anaesthetic and sedative (opioid) products

for companion animals in Australia.[2] The ACCC does not indicate any unresolved concerns in relation to this market definition.

28. Please let us know if you would like to meet to discuss.

Yours sincerely

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[2] https://www.accc.gov.au/system/files/public-registers/documents/Zoetis%20proposed%20acquisition%20of%20Jurox%20-%20Statement%20of%20Issues.pdf

APPENDIX 1: SPECIFIC RESPONSES BY ZOETIS TO SPECIFIC STATEMENTS IN THE STATEMENT OF UNRESOLVED ISSUES

Statement in SOUI	Zoetis response
32. In the SOI, we defined a market for opioid-based pre-anaesthetics for companion animals. Based on further analysis, we now consider there is a national market for the manufacture/importation and wholesale supply of butorphanol-based sedatives for companion animals. Butorphanol is an opioid.	The active ingredient-based distinction is artificial and does not reflect practice or clinical reality. Zoetis urges the Commission to test the proposed market definition with practicing veterinarians, and the practical requirements for pre-anaesthetic sedation.
33. With regard to the product market, we consider that other products (including products with an opioid active ingredient) are not sufficiently close substitutes for butorphanol-based sedatives on either the supply or the demand side such that they fall within the same market.	This is contrary to widely accepted and well-established veterinary guidance, the academic literature and Zoetis' experience, as set out above.
33.1 On the demand side, there are no close substitutes for butorphanol-based sedatives for companion animals:	There are substitutes, and a clinician approaches sedation through a therapeutic lens, rather than a focus on active ingredients or products.
33.1.3 butorphanol sedatives have different indications and usage than other opioid-based products; and	While butorphanol is registered on the ACVM register as being used in pre-anaesthetic and sedative combinations, buprenorphine is also commonly used by vets in this way, as is established in Grint et al. 2010; Hunt et al. 2013; and Warne et al. 2014. Methodone, morphine, and fentanyl are available in New Zealand for use as an opioid sedative (see the tables above).
33.1.4 butorphanol sedatives indicated for horses or for humans are not typically used to treat companion animals	Zoetis is unaware of human butorphanol products available for use in veterinary medicine. There are, however, human buprenorphine products that are actively wholesaled to veterinarians. [ ]. The ACVM product use cascade in the SOUI (p.6) would refer veterinarians to the use of an "off label" veterinary product where an on-label product was unavailable.

Statement in SOUI	Zoetis response
33.2 On the supply side, suppliers of other products cannot easily switch to supplying butorphanol sedatives indicated for use on companion animals due to the time and costs involved in developing, manufacturing and marketing a product and obtaining ACVM registration.	These markets are now genericised, and generic companies (such as Troy and Jurox) have not encountered difficulty entering and competing in this market. The products can be sourced elsewhere, including because: 1. the opioids are very old products and their production is not protected by trade secrets or patents; and 2. the higher level of regulation is not a barrier, as supply chains routinely handle such products. The cost of development, manufacturing and marketing a product, and obtaining ACVM registration is not a barrier, including because: 1. the cost of "developing" a generic is low: copying an originator's product is easy, and part of the core business of generic companies such as Troy and Jurox, as is the well-established and comparatively cheap registration process for ACVM; 2. the products can be sourced from a contract manufacturer, meaning there is no manufacturing "cost" for a generic company if it does not wish to manufacture the product itself. The pharmaceutical industry is global, and contract manufacturers can be located anywhere in the world;

Statement in SOUI	Zoetis response
	3. any marketing will be minimal, or non-existent, because it is a generic product so the sales focus will be on price, and because butorphanol is a prescription product it cannot be advertised to the public. Any marketing costs would be comparable with other generic prescription products and, depending on the deal between the generic company and NZ wholesalers, that cost may be absorbed by the wholesaler.
43. In the application, Zoetis used a relevant market that included opioid sedative products containing the active ingredient buprenorphine. However, we understand that opioid products containing buprenorphine have different indications as those containing butorphanol are used for different purposes. For example: 43.1 several vets advised that buprenorphine primarily acts as an analgesic, providing pain relief, while butorphanol primarily acts as a sedative; and 43.2 a supplier of a buprenorphine product told us that it competes with other products containing buprenorphine and is not used as a pre-anaesthetic or a sedative.	As illustrated in the tables taken from guidelines above, buprenorphine can be used as part of the pre-anaesthetic protocol (and is commonly used in combination with a tranquiliser such as Acepromazine). Further evidence for the use of buprenorphine in this way, in addition to the anaesthesia guidelines, can be noted in the following peer reviewed publications Grint et al. 2010; Hunt et al. 2013; Warne et al. 2014. Whereas product managers will focus on driving sales in particular areas, it is the veterinarians who understand the substitutability of the products. Paragraph 43.2 appears to contradict the ACVM registrations and guidance; vets will use opioids interchangeably for their analgesic and sedative properties. Zoetis refers the Commerce Commission to the guidelines and studies highlighting the use of buprenorphine as a pre-anaesthetic agent and in the place of butorphanol in sedative protocols.

Statement in SOUI	Zoetis response
46. As set out in the background section, the ACVM strongly recommends that veterinarians follow the on-label indications of each animal health care product and must have a good reason to use an off-label product. The Vet Council Code of Professional Conduct makes a similar recommendation. If so, products indicated for use in other animals are not likely to be a close substitute for those indicated for companion animals. While it is possible that some veterinarians could ignore this advice, at this point we have received limited evidence that this is common practice.	[ ]. In practice: - human products are sold to veterinarians; - those products are used in animals; and - [ ]. [ ].
47. The products that Zoetis identified are unlikely to be close substitutes for the following reasons: 47.1 Vetergesic contains a different active ingredient (buprenorphine) and is indicated for the relief of post-operative pain in a dog or cat (that is, it is not used for sedation); 47.2 Dolorex is indicated for horses; and 47.3 Temgesic is indicated for humans, contains a different active ingredient (buprenorphine) and is used for pain relief (that is, it is not used for sedation).	[ ].