

5.13 TRAMADOL HYDROCHLORIDE WITH PARACETAMOL, Tablet containing tramadol hydrochloride 37.5 mg with paracetamol 325 mg, Zaldiar[®], Aspen Pharmacare Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a Section 85, Restricted Benefit listing for the fixed dose combination (FDC) of tramadol 37.5 mg/paracetamol 325 mg for treatment of acute and chronic pain. The FDC of tramadol 37.5 mg/paracetamol 325 mg has not been considered by the PBAC previously. The Pre-Sub-Committee Response (PSCR) proposed restricting the use of the FDC of tramadol 37.5 mg/paracetamol 325 mg to acute pain only, with a Maximum Quantity of 20 and 2 repeats (compared with no repeats in the original proposal). The ESC acknowledged this change to the proposed listing but considered that despite this change if the proposed FDC was listed substantial leakage to use in chronic pain would be likely, therefore issues raised specific to use in chronic pain may still be relevant.
- 1.2 The basis for the submission was a cost-minimisation analysis against tramadol 50 mg IR.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients requiring pain medication for acute and chronic treatment.
Intervention	Fixed dose combination (FDC) tablet: tramadol 37.5 mg/paracetamol 325 mg
Comparator	Tramadol 50 mg immediate release (IR). Contrary to the PBAC Guidelines for FDCs, the submission did not present a comparison against the individual components used concomitantly. In addition, tramadol 50 mg is only PBS listed for dose titration in the chronic pain setting, and there may be other comparators that are also appropriate.
Outcomes	Clinical: Pain intensity, pain relief rating scales, SF-36, WOMAC, Investigator and subject overall assessment Safety: Key safety outcomes: AEs and discontinuations due to AEs
Clinical claim	FDC of tramadol 37.5 mg/paracetamol 325 mg is non-inferior to tramadol 50 mg in terms of efficacy and superior in terms of safety. The claim against tramadol 50 mg appears to be supported by the evidence in acute pain. However, it is not adequately supported in chronic pain. The submission did not present sufficient evidence to form a claim against the individual components used concomitantly, or other potentially appropriate comparators.

Table 1-1 p22 and text Section 2.8.2 p221 of the submission.

Abbreviations: AE = adverse event; FDC = fixed dose combination; IR = immediate release; SF-36 = Short-Form 36-item survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Acute pain					
TRAMADOL 37.5 MG/ PARACETAMOL 325 MG film coated tablets, 20	1	20	2	\$13.09	Zaldiar® Aspen Pharmacare Australia Pty Ltd
Category/Program:	General Schedule				
Clinical criteria:	The condition must be one in which aspirin and/or paracetamol alone are inappropriate or have failed.				

- 2.1 The requested restriction was for patients that require treatment for acute or chronic pain, limited to acute pain in the PSCR, where aspirin and/or paracetamol alone are inappropriate or have failed. The population is consistent with the restriction of the nominated primary comparator for acute pain. However, the circumstances of use are broader than those of the nominated comparator; in patients with chronic pain tramadol 50 mg IR is only indicated for dose titration. The ESC considered that if listed with a restriction to acute pain, there is potential for leakage to chronic pain, where the doses in the proposed FDC are unlikely to be appropriate.
- 2.2 The PSCR also requested that the number of repeats for the requested listing in acute pain be increased to two. Based on the PI maximum of 8 tablets daily this equates to just over one week of supply. This is inconsistent with the submission's nominated primary comparator, tramadol 50 mg IR, which does not allow repeat scripts to be filled (PBS item number: 5232J and 8455B) and only provides 20 capsules per supply for acute pain.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 The FDC of tramadol 37.5 mg/paracetamol 325 mg was TGA registered on the 19th of March 2012 for the indication of moderate pain. Tramadol was first registered in 1998 (AusPAR September 2012).

Previous PBAC consideration of OTC pain medications

- 3.2 There are a range of formulations of tramadol currently subsidised on the PBS including sustained release (SR) tablet formulations in multiple strengths (50 mg, 100 mg, 150 mg and 200 mg), oral liquid, and injections. Although tramadol and its FDC formulation have been registered on the ARTG for a considerable time, there are no formulations of tramadol available as an FDC on the PBS.

- 3.3 Based on specific advice from the PBAC, over-the-counter (OTC) medicines, including paracetamol, that were available to Australian patients at a reasonable cost in the absence of PBS subsidy were removed from general availability on the PBS on 1 January 2016. The PBAC recommended paracetamol 665 mg tablets remain listed for use in palliative care and Aboriginal and/or Torres Strait Islander patients with persistent pain associated with osteoarthritis¹.
- 3.4 As of the 1st of February 2018, all medicines containing codeine will be available by prescription only. The Standard for the Uniform Scheduling of Medicines and Poisons (the Poisons Standard) will be amended to delete the codeine entries from Schedule 2 (Pharmacy Medicines) and Schedule 3 (Pharmacist Only Medicines), leaving the codeine entries in Schedule 4 (Prescription Only Medicine) and Schedule 8 (Controlled Drug) only from the 1st February 2018 onwards. This may have implications for the volume of PBS prescriptions for codeine products or their alternatives, such as tramadol.

4 Population and disease

- 4.1 Pain exists as an acute or chronic condition. Acute pain lasts for a short time, generally occurs suddenly, and can result from disease, inflammation or tissue injury. Chronic pain lasts beyond the time expected for healing, and may follow surgery, trauma or be caused by another condition. Chronic pain can be continuous or recurrent and it adversely impacts an individual's well-being, and functional ability.
- 4.2 Both pharmacological and non-pharmacologic approaches are used to treat acute and chronic pain. Pharmacological options include a variety of drug types such as non-opioid analgesics (acetaminophen [paracetamol], non-steroidal anti-inflammatory drug [NSAID], serotonergic drugs), and opioids. The FDC of tramadol 37.5 mg/paracetamol 325 mg is proposed for use in patients that require treatment for acute or chronic pain, limited to acute pain only in the PSCR, where aspirin and/or paracetamol alone are inappropriate or have failed.
- 4.3 Treatment guidelines (eTG Complete) recommend that in patients presenting with moderate pain that is not adequately relieved by paracetamol and/or an NSAID, and the pain is interfering with the patients' quality of life, to consider adding an oral opioid (codeine, tramadol IR, or oxycodone IR). However, there appears to be some concern regarding the place of tramadol in the management of pain in adults (CADTH report 2015). The role of tramadol in managing pain is limited, due to its limited analgesic activity, adverse effects and drug interactions, particularly with serotonergic drugs that may be beneficial in chronic pain management (eTG Complete). The PSCR noted that as per eTG Complete Analgesic Guidelines tramadol 50mg IR 50-100mg orally up to four times daily is recommended as a suitable Step 2

¹ Other matters, 2016-03, March 2016 PBAC Meeting, URL: www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2016-03/other-matters-2016-03.docx

treatment option that can be added to paracetamol therapy if pain relief is insufficient in moderate acute pain. However this recommended dosing differs from that in the FDC. ESC noted it would be best practice for patients with acute pain to be treated with a higher dose of paracetamol than that contained in the FDC before considering adding an oral opioid such as tramadol.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated tramadol 50 mg IR as the main comparator for both acute and chronic pain. The FDC of paracetamol 500 mg/codeine phosphate 30 mg was nominated as a secondary economic comparator only.
- 5.2 Tramadol 50 mg IR may not be the only appropriate main comparator because:
- Although the comparison is informative for acute pain as the IR formulation is contained in the FDC, only tramadol sustained release (SR) formulations are reimbursed for ongoing use in chronic pain. The PBS listing for tramadol 50 mg IR in chronic pain is as a Restricted Benefit Item which specifies use in titration only;
 - There are NSAIDs available over the counter that are recommended as treatments for moderate pain (eTG Complete, URL: <https://tgldcdp.tg.org.au>);
 - Although paracetamol is not listed on the PBS as a General Benefit item, it is available as an OTC medication and *should* be administered with tramadol concomitantly according to national and international pain guidelines. Tramadol and paracetamol as individual components administered concomitantly may be considered to be a more appropriate comparison. ESC agreed that this is the most appropriate comparator for the FDC.
- 5.3 For the treatment of chronic pain, tramadol SR tablets are less expensive than the FDC of tramadol 37.5 mg/paracetamol 325 mg and are alternative therapies because they could be replaced in practice. If treatment with the FDC of tramadol 37.5 mg/paracetamol 325 mg costs more than an alternative therapy or alternative therapies, the PBAC could only recommend listing of the FDC of tramadol 37.5 mg/paracetamol 325 mg if it is satisfied that the FDC of tramadol 37.5 mg/paracetamol 325 mg provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953, Section 101(3B)*). The ESC noted that where leakage to use in chronic pain occurs for the proposed listing costs would be higher than for the alternative treatments available for chronic pain, resulting in an increased cost to the PBS.
- 5.4 The submission did not present a comparison against the individual components used concomitantly. The PSCR stated that RCT data from 8 studies comparing the

proposed FDC with the individual components was meta-analysed and presented in Attachment 4 to the submission. However, the meta-analyses in Attachment 4 provided a comparison of the FDC with its individual components given separately (in separate arms of the trials), not concomitantly as is requested under the FDC guidelines. The ESC considered that concomitant use of the components is the most appropriate comparator, particularly as use of tramadol 50 mg IR is recommended by national and international guidelines together with a step 1 analgesic such as paracetamol. The chosen comparator in the submission does not represent best practice.

- 5.5 For the treatment of acute pain, the FDC of paracetamol 500 mg/codeine phosphate 30 mg was provided as a secondary economic comparator. This is an appropriate comparator for this submission as it could be replaced in practice. Based on review of the therapeutic relativity sheets, the submission reasoned that since tramadol 50 mg was recommended on the basis of acceptable cost-effectiveness compared with the FDC of paracetamol 500 mg and codeine phosphate 30 mg, and with codeine phosphate 30 mg alone, the FDC of tramadol 37.5 mg/paracetamol 325 mg is also cost-effective compared to codeine based regimens. This assertion is only valid if the FDC of tramadol 37.5 mg/paracetamol 325 mg is considered to be non-inferior to tramadol 50 mg. A clinical comparison of tramadol 37.5 mg/paracetamol 325 mg with codeine phosphate 30 mg/ paracetamol 500 mg was not presented in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one health care professional via the Consumer Comments facility on the PBS website. The comment described the need for available treatments for patients with chronic pain.

Clinical trials

- 6.3 The submission was based on three head-to-head trials comparing the FDC of tramadol 37.5 mg/paracetamol 325 mg to tramadol 50 mg IR for treatment of acute pain (ZAL-06, CAPSS-241, and GRTF-ZAL-1), and an indirect comparison of the FDC of tramadol 37.5 mg/paracetamol 325 mg with tramadol 50 mg IR, using placebo as the common comparator for treatment of chronic pain. The submission presented nine randomised controlled trials (RCTs) as the basis of the indirect treatment comparison (CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013, CAPSS-051, CA-R0027).

6.4 Details of the trials presented in the submission are provided in the table below.

6.5 In addition to the trials presented in the submission the sponsor's Pre-PBAC response provided a description of a single centre RCT comparing the FDC of tramadol 37.5 mg/paracetamol 325 mg with concomitant tramadol 50 mg IR plus paracetamol 500 mg².

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
FDC the FDC of tramadol 37.5 mg/paracetamol 325 mg vs tramadol 50 mg IR		
ZAL-06	ZAL-06: A randomized, multi-center, double-blind, double-dummy, parallel group clinical study assessing the effectiveness and tolerability of oral tramadol HCl 37.5 mg/paracetamol 325 mg compared with tramadol HCl 50 mg in day-care hand-surgery patients	Grunenthal. Internal study report, 17 June 2009
	Rawal, N., et al. (2011). Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial.	Journal of Pain Research. 2011, 4: 103-110.
CAPSS-241	CAPSS-241: A comparison of the efficacy and safety of ultracet™ (tramadol hcl/acetaminophen) versus ultram® (tramadol hcl) versus placebo in subjects with pain following oral surgery.	Ortho-McNeil Pharmaceutical. Internal study report 7 February 2003.
	Fricke, J.R., Jr., Hewitt, D.J., et al. (2004). "A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain."	Pain. 2004, 109(3): 250-257.
GRTF-ZAL 1	GRTF-ZAL 1: A comparison of patient satisfaction with the association tramadol HCl (37,5 mg) plus paracetamol (325 mg) versus tramadol (50 mg) for the treatment of subacute low back pain.	Grunenthal. Internal study report, 28 June 2002
	Perrot, S., Krause, D., et al. (2006). Efficacy and tolerability of paracetamol/tramadol (325 mg/37.5 mg) combination treatment compared with tramadol (50 mg) monotherapy in patients with subacute low back pain: A multicenter, randomized, double-blind, parallel-group, 10-day treatment study."	Clin Ther. 2006, 28(10): 1592-1606.
FDC the FDC of tramadol 37.5 mg/paracetamol 325 mg vs placebo		
CAPSS-104	CAPSS-104: A comparison of the analgesic efficacy and safety of Tramadol HCL/Acetaminophen versus placebo for the symptomatic treatment of the pain and function of osteoarthritis. .	Ortho-McNeil Pharmaceutical. Internal study report 03 August 2001.
CAPSS-112	CAPSS-112: A comparison of the analgesic efficacy of Tramadol hcl/acetaminophen versus placebo for the treatment of chronic lower back pain.	Ortho-McNeil Pharmaceutical. Internal study report 20 August 2001.
	Ruoff, G. E., N. Rosenthal, D. Jordan, R. Karim, M. Kamin and C.-S. G. Protocol (2003). Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study.	Clinical therapeutics. 2003, 25(4): 1123-1141.

² Sawaddiruk, Paibonworachat et al. (2010). Comparison of Efficacy and Effectiveness between ULTRACET™ and Tramadol/Acetaminophen in Acute Postoperative Pain after Upper Extremity Surgery. J Med Assoc Thai; 93(7): 821-7.

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Trial ID	Protocol title/ Publication title	Publication citation
CAPSS-113	CAPSS-113: A comparison of the analgesic efficacy of Tramadol hcl/acetaminophen versus placebo in subjects with the pain of fibromyalgia.	Ortho-McNeil Pharmaceutical. Internal study report 20 August 2001.
	Bennett, R. M., M. Kamin, R. Karim and N. Rosenthal (2003). Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study.	The American journal of medicine. 2003, 114(7): 537-545
	Bennett, R. M., J. Schein, M. R. Kosinski, D. J. Hewitt, D. M. Jordan and N. R. Rosenthal (2005). "Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen."	Arthritis and rheumatism. 2005, 53(4): 519-527.
TRP-CAN-1	PRI/TRP-CAN-1: A comparison of the analgesic efficacy of Tramadol hcl/acetaminophen (tramadol/apap) versus placebo for the treatment of chronic lower back pain.	Ortho-McNeil Pharmaceutical. Internal study report 01 February 2002.
	Peloso, P. M., L. Fortin, A. Beaulieu, M. Kamin, N. Rosenthal and T. R. P. C. A. N. S. G. Protocol (2004). "Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial."	The Journal of rheumatology. 2004, 31(12): 2454-2463.
CAPSS-237	CAPSS-237: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Tramadol HCl/Acetaminophen for the Treatment of Painful Diabetic Neuropathy.	PriCara (Unit of Ortho-McNeil). Internal study report 19 December 2005.
	Freeman, R., P. Raskin, D. J. Hewitt, G. J. Vorsanger, D. M. Jordan, J. Xiang and N. R. Rosenthal (2007). "Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy."	Curr Med Res Opin. 2007, 23(1): 147-161.
CAPSS-114	CAPSS-114: A comparison of the analgesic efficacy and safety of Tramadol hcl/acetaminophen versus placebo for the treatment of the signs and symptoms of osteoarthritis in subjects receiving a cox-2 selective inhibitor.	Ortho-McNeil Pharmaceutical. Internal study report. 26 July 2001.
	Emkey, R., N. Rosenthal, S. C. Wu, D. Jordan and M. Kamin (2004). "Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial."	J Rheumatol. 2004, 31(1): 150-156.
Chang 2013	Chang, J. K., C. T. Yu, M. Y. Lee, K. Yeo, I. C. Chang, H. K. Tsou and J. C. Wei (2013). "Tramadol/acetaminophen combination as add-on therapy in the treatment of patients with ankylosing spondylitis."	Clin Rheumatol. 2013, 32(3): 341-347.
	Wei, J. C. and J. K. Chang (2010). "Tramadol/acetaminophen (Ultracet) had add-on effect to non-steroidal anti-inflammatory drugs in patients with ankylosing spondylitis." International	Journal of Rheumatic Diseases, 2010. 13: 152.
Tramadol 50 mg IR vs placebo		
CAPSS-051	CAPSS-051: A comparison of analgesic efficacy and safety of Ultram (tramadol HCl) versus placebo for the treatment of the pain of osteoarthritis.	Ortho-McNeil Pharmaceutical. Internal Study Report. 09 March 1999.
	Fleischmann, R. M., J. R. Caldwell, S. H. Roth, J. R. P. Tesser,	Current Therapeutic Research. 2001,

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Trial ID	Protocol title/ Publication title	Publication citation
	W. Olson and M. Kamin (2001). "Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial."	62(2): 113-128.
CA-R0027	CA-R0027: A placebo controlled trial of Ultram (Tramadol HCL) for Painful Diabetic Neuropathy (Protocol TPS DN).	Ortho-McNeil Pharmaceutical. Internal Study Report. 25 November 1997.
	Harati, Y., C. Gooch, M. Swenson, S. Edelman, D. Greene, P. Raskin, P. Donofrio, D. Cornblath, R. Sachdeo, C. O. Siu and M. Kamin (1998). "Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy."	Neurology. 1998, 50(6): 1842-1846.

Source: Table 2-4 pp54-56, of the submission. See Attachment 2 Table 2.2.1 of the Commentary for list of trials comparing FDC the FDC of tramadol 37.5 mg/paracetamol 325 mg vs tramadol 37.5 mg IR vs paracetamol 325 mg.

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
FDC the FDC of tramadol 37.5 mg/paracetamol 325 mg vs tramadol 50 mg IR					
ZAL-06	261	R, DB, MC, PC, PG, 2 days	Unclear - high	Acute pain caused by surgical procedure	Treatment satisfaction using a 4-point verbal rating scale (VRS); Average pain intensity using an 11-point numerical rating scale (NRS); safety; discontinuation
CAPSS-241	450	R, DB, Single-centre, PG, 6 hours	Unclear - high	Acute pain caused by surgical procedure	Total pain relief (TOTPAR), sum of pain intensity differences (SPID) and sum of pain intensity differences (SPRID); safety; discontinuation
GRTF-ZAL 1	119	R, DB, MC, PC, PG, 10 days	Low – unclear	Subacute low back pain	Patient satisfaction using a 4-step scale; Pain relief on a 5-point Likert scale; Pain intensity using a 100 mm visual analogue pain scale (PVA); safety; discontinuation
Meta-analysis		Efficacy outcomes were not meta-analysed due to heterogeneity across trials. Safety outcomes were pooled.			
FDC the FDC of tramadol 37.5 mg/paracetamol 325 mg vs placebo					
CAPSS-104	321	R, DB, MC, PC, PG, 91 days	Unclear	Osteoarthritis of knee ≥ 1 year; PVA Score ≥ 40 mm	Patient overall assessment of study medication using a 5-point rating scale; Pain intensity using a 100 mm PVA; Pain relief using a 6-point Likert scale; SF-36; WOMAC; safety; discontinuation
CAPSS-112	322	R, DB, MC, PC, PG, 91 days	Unclear	Chronic lower back pain; PVA Score ≥ 40 mm	Patient overall assessment of study medication using a 5-point rating scale; Pain intensity using a 100 mm PVA; Pain relief using a 6-point Likert scale; SF-36; discontinuation
CAPSS-113	315	R, DB, MC, PC, PG, 91 days	Unclear	Fibromyalgia; PVA Score ≥ 40 mm	Pain intensity using a 100 mm PVA; Pain relief using a 6-point Likert scale SF-36; discontinuation
TRP-CAN-1	338	R, DB, MC, PC, PG, 91 days	Unclear	Chronic lower back pain; PVA Score ≥ 40 mm	Patient overall assessment of study medication using a 5-point rating scale; Pain intensity using a 100 mm PVA; Pain relief using a 6-point Likert scale; SF-36; discontinuation
CAPSS-237	313	R, DB, MC, PC, PG, 66 days	Unclear	Painful diabetic neuropathy in the lower extremities Daily pain for ≥ 3 mth	Pain intensity using a 100 mm PVA; SF-36; discontinuation
CAPSS-114	307	R, DB, MC, PC, PG, 91 days	Unclear	Symptomatic osteoarthritis of the knee or hip ≥ 1 year; PVA Score > 50 mm	Patient overall assessment of study medication using a 5-point rating scale; Pain intensity using a 100 mm PVA; Pain relief using a 6-point Likert scale SF-36; WOMAC; safety; discontinuation
Chang 2013	60	R, DB, Single-centre, PC, 84 days	Unclear	Active ankylosing spondylitis; BASDAI level > 3	ASAS20; Pain VAS; SF-36; safety; discontinuation
Meta-analysis		<ul style="list-style-type: none"> Patient overall assessment of study medication using a 5-point rating scale; CAPSS-104, 			

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
CAPSS-112, TRP-CAN-1. • Pain intensity using a 100 mm PVA; CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114. • Pain relief using a 6-point Likert scale; CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-114. • SF-36; CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013. • WOMAC; CAPSS-104 and CAPSS-114. • Safety and AEs; CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013. • Discontinuation (all, due to AE, due to lack of efficacy); CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013.					
Tramadol 50 mg IR vs placebo					
CAPSS-051	129	R, DB, MC, PC, PG, 91 days	Unclear to high	Symptomatic osteoarthritis of knee \geq 1 year, at least moderate pain.	Patient overall assessment of study medication using a 5-point rating scale; Pain intensity 5-point Likert scale; Pain relief using a 7-point Likert scale; WOMAC; safety; discontinuation
CA-R0027	131	R, DB, MC, PC, PG, 42 days	Unclear to high	Distal symmetric diabetic neuropath; Daily pain in lower extremities for \geq 3 mth	Pain intensity 5-point Likert scale; Pain relief using a 6-point Likert scale; safety; discontinuation
Meta-analysis		• Pain intensity using a 5-point Likert; CAPSS-051 and CA-R0027 • SF-36; CAPSS-051 and CA-R0027 • Safety and AEs; CAPSS-051 and CA-R0027 • Discontinuation (all, due to AE, due to lack of efficacy); CAPSS-051 and CA-R0027			

Abbreviations: DB= double blind; CVD= cardiovascular disease; MC=multi-centre; mth= month; n = number of participants with event; N = total participants in group; NSAID= nonsteroidal anti-inflammatory drug; R= randomised; PG= parallel group; PVA= visual analogue pain scale; T37.5+P325, the FDC of tramadol 37.5 mg/paracetamol 325 mg; T50, tramadol 50 mg; pbo, placebo;
 Source: Table 2-10 p63, Table 2-16 p71, Table 2-23 p96, and Table 2-29 pp108-112, Table 2-14 p68, Table 2-18 p76, Table 2-19 pp77-88, text p99, Table 2-37 pp135-138 of the submission.

6.7 The trials in acute pain (ZAL-06, CAPSS-241, GRTF-ZAL 1) were subject to detection/other bias due to the method of pain management and permitted concomitant medications during the trials. There was considerable heterogeneity of the trials in terms of their presenting conditions, dosing schedules, duration, and use of tramadol in titration. For instance, patients in ZAL-06 were administered many other concomitant medications during the 2 days patients were observed, which may have influenced the participants' perceptions of the efficacy of the study medication administered. CAPSS-241 was a single centre study, only 6-hours in duration, and patients were only administered two tablets. This trial was subject to a high degree of bias.

6.8 The differences pertaining to study design characteristics and placebo response rates in the trials of chronic pain (CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013, CAPSS-051, CA-R0027) are likely to have impacted on the transitivity of the trials in the indirect comparison. The trials in chronic pain were subject to attrition bias, as the proportion of patients discontinuing the trials was

high, and ranged from 25% to 74% in the placebo arms. The differences between trials pertaining to the dosing schedules, given that patients are able to self-titrate to achieve an analgesic effect, and differences in concomitant medications in potentially affecting the performance with respect to pain management are likely to have impacted on their transitivity. The degree to which the results of the indirect comparison would have been affected is unclear.

- 6.9 The tramadol IR formulation was used in the FDC as part of ongoing medication in the trials of chronic pain (CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013). However, in Australia, the tramadol SR formulation, which lasts for 12 hours and is administered less frequently, is used in chronic pain. It has a general indication for the treatment of pain. The tramadol IR formulation is listed on the PBS for use in acute pain and for dose titration in chronic pain. Therefore, in chronic pain, the proposed listing of the FDC is broader and therefore inconsistent with that being currently applied to tramadol 50 mg IR, which is PBS listed for titration in patients with chronic pain. The PSCR limited the restriction to acute pain.

Comparative effectiveness

- 6.10 A summary of the effectiveness of the FDC of tramadol 37.5 mg/paracetamol 325 mg to tramadol 50 mg IR in patients with acute pain is provided in Table 4 to Table 6, and for chronic pain in Table 8 to Table 10.

Acute pain

- 6.11 The submission claimed that there were no differences in the outcomes of treatment satisfaction, overall assessment of study medication, and change in pain intensity, and improved pain relief with the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR groups in the treatment of acute pain.
- 6.12 The mean difference in responder treatment satisfaction in ZAL-06 was 6.25 (95% CI -4.33, 16.83) and in GRTF-ZAL 1 was 5.7% (95%CI: -11.2%, 22.2%). Based on the non-inferiority margin of 20%, the submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was non-inferior to tramadol 50 mg IR. The lower confidence interval did not exceed 20% non-inferiority margin proposed by the submission.

Table 4: Overall assessment of study medication and treatment satisfaction across the acute pain trials

Trial ID	T37.5+P325	T50	Outcome
ZAL-06 (Day 2) ^a	100/128 (78.1)	92/128 (71.9)	Responders treatment satisfaction
Diff (95%CI), p-value	6.25 (-4.33, 16.83), p = 0.2420		
ZAL-06 (Day 2) ^b , n/N (%)	103/128 (80.4)	98/128 (76.5)	Treatment satisfaction ^b
Excellent ^b	46/128 (35.9)	46/128 (35.9)	
Good ^b	57/128 (44.5)	52/128 (40.6)	
CAPSS-241 (6 hours) ^{c,e}	45/151 (29.8)	16/149 (10.7)	Subjects Overall Medication Assessment
Excellent	14/151 (9.3)	2/149 (1.3)	
Very good	31/151 (20.5)	14/149 (9.2)	
GRTF-ZAL 1 (10 days) ^d	41/59 (69.5)	37/58 (63.8)	Last patient satisfaction score
RD (95% CI)	5.7% (-11.2%, 22.2%)		
Very satisfied	15/59 (25.4)	20/58 (34.5)	
Satisfied	26/59 (44.1)	17/58 (29.3)	

Source: ZAL-06 Table 2-38 p140, Table 2-39 p141, Table 2-40 p142 of the submission; CAPSS-241 Table 2-50 p153 of the submission; GRTF-ZAL 1 Table 2-51 p154 of the submission.

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group; RD = risk difference

Notes: Data are reported as n/N (%) unless stated otherwise. a ZAL-06: assessed on a 4-point verbal rating scale (VRS) (3=excellent, 2=good, 1=fair, or 0=poor). Treatment response rate was judged as excellent or good, and no rescue medication of analgesic concomitant medication taken before 24:00 on the first post-operative day. b ZAL-06: assessed on a 4-point verbal rating scale (VRS) (3=excellent, 2=good, 1=fair, or 0=poor) on Day 2, 1st post-operative day, Did not include caveat of rescue medication in the definition which differs from the definition of Responder. The sum of the Excellent and Good categories for ZAL-06 do not sum to the Day-2 totals for the FDC: figures reported are as shown in the submission. c CAPSS-241: assessed on a 5-pt rating scale (5=excellent, 4=very good, 3=good, 2=fair, 1=poor). d GRTF-ZAL 1: assessed on a 4-point rating scale (very satisfied, satisfied, dissatisfied, very dissatisfied). e T37.5+P325 vs T50, p<0.001, Wilcoxon-Mann-Whitney Test.

6.13 The submission claimed there was no treatment difference in pain intensity between the FDC of tramadol 37.5 mg/paracetamol and tramadol 50 mg IR, based on the following:

- There was no difference in the average pain intensity in ZAL-06 as measured on the NRS 11-point Likert scale between FDC of the of tramadol 37.5 mg/paracetamol 325 mg in the evening of Day 1 (-0.2137, 95%CI: -0.7919, 0.3645), and on the evening of Day 2 (-0.1336, 95%CI: -0.6514, 0.3843). Based on the non-inferiority margin of the upper 95%CI being less than 0.4, the submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was non-inferior to tramadol 50 mg IR.
- In CAPSS-241, after 6 hours patients treated with the FDC of tramadol 37.5 mg/paracetamol 325 mg obtained more pain relief compared with tramadol 50 mg IR (p<0.001).
- In GRTF-ZAL 1, there were no differences between the treatment groups in reduction of pain intensity after 10 days of treatment with the FDC of tramadol 37.5 mg/paracetamol 325 mg (1.23, 95% CI: -7.41, 9.97). Based on a non-inferiority margin of the upper CI being less than 14-17 mm (visual analogue scale), the submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was non-inferior to tramadol 50 mg IR.

Table 5: Change in pain intensity across the acute trials (continuous outcomes)

Trial ID	T37.5+P325		T50		Mean diff. ^g (95% CI)	Test
	Baseline mean (SD)	End of study mean (SD)	Baseline mean (SD)	End of study mean (SD)		
ZAL-06 ^a	2.7 (2.2)	1.7 (2.0)	2.9 (2.6)	1.7 (2.0)	-0.13 (-0.65, 0.38), p=0.6118	ANOVA: 11 pt. Likert
CAPSS-241		n=72		n=25		
PID ^b	NR ^c	0.5 (0.78)	NR ^c	0.2 (0.55)	p<0.001 ^e	4-pt Likert
SPID ^d	NR ^c	3.1 (3.57)	NR ^c	0.6 (2.65)	p<0.001 ^e	
GRTF-ZAL 1 ^f	N=59 65.6 (13.4)	N=55 29.0 (22.5)	N=58 64.5 (14.0)	N=55 27.8 (23.3)	1.23 (-7.41 to 9.87) p=0.9634	100 mm VAS

Source: ZAL-06 Table 2-42 p143 of the submission; CAPSS-241 CSR Table 8 p50; GRTF-ZAL 1 Table 2-52 p155 of the submission; Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; PID= pain intensity difference; SD = standard deviation; SPID= sum of pain intensity differences; VAS = visual analogue scale.

Notes: ^a ZAL-06: '0' corresponds to 'no pain', '10' corresponds to 'pain as bad as you can imagine'; Results by NRS 11-pt likert category are provided in the submission in Table 2-43. ^b CAPSS-241: Pain Intensity Rating Scale: 0=none, 1=mild, 2=moderate, 3=severe. ^c Baseline pain intensity reported categorically, see Table 2.4.3 Attachment 2 of the Commentary. More patients had severe pain in tram50 group compared with FDC (34.2% vs 28.1%); Study criteria for entry were that patients had moderate pain (PID=2). ^d CAPSS-241: SPID Scale: -6 = pain not better than baseline at every evaluation; 18 = complete relief from severe baseline pain at every evaluation. ^e Mean difference between groups was not reported in the submission, CSR or the publication; only the p-values were reported. ^f GRTF-ZAL 1: PVA 0-100; 0=no pain to 100=worst possible pain. ^g Mean difference between groups at the end of study.

6.14 The submission claimed the FDC provided more pain relief than tramadol 50 mg at all time intervals in CAPSS-241 (p<0.001). It was unclear from CAPSS-241 whether it was the paracetamol component providing relief over the 6-hour period. There was no treatment difference in pain relief between the FDC of tramadol 37.5 mg/paracetamol and tramadol 50 mg IR after ten days of treatment in GRTF-ZAL 1.

Table 6: Change in pain relief across the acute pain trials

Trial ID	T37.5+P325	T50
ZAL-06 (Day 2) ^a	NR	NR
CAPSS-241 (6 hours)	mean (SD)	mean (SD)
Mean PAR ^a , 6 hrs	n=72 1.1 (1.38)	n=25 0.5 (1.13)
TOTPAR ^b :AUC 6 hrs	7.4 (6.3)	2.5 (5.1)
GRTF-ZAL 1 (10 days) ^c	n/N (%)	n/N (%)
None	4 /59 (6.8)	4 /58 (6.9)
Slight	7/59 (11.9)	7/58 (12.1)
Moderate	15/59 (25.4)	5/58 (8.6)
Important	17/59 (28.8)	22/58 (37.9)
V. important	12/59 (20.3)	16/58 (27.6)
Not specified	4/59 (6.8)	4/58 (6.9)

Source: CAPSS-241 Table 2-46 p148 of the submission, CSR Table 7 p48; GRTF-ZAL 1 Table 2-53 p156 of the submission
Abbreviations: AUC= area under the curve; CI = confidence interval; n = number of participants with event; N = total participants in group; NR= not reported; PAR = pain relief; TOTPAR = total pain relief.
Notes: ^a CAPSS-241: 5 pt likert: 4=complete, 3=a lot, 2=some

6.15 An overview of the results presented in the trials in acute pain is presented in Table 7. The ESC noted that applicability of these results to the clinical setting where tramadol 50mg IR is also used in combination with paracetamol was not clear.

Table 7: Outcomes reported across the acute pain trials

Acute pain			
T37.5+P325 vs T50			
	ZAL-06 (2 days)	CAPSS-241 (6 hours)	GRTF-ZAL 1 (10 days)
Pain intensity			
MCID: Likert 11-pt: 1 or 2 pts or 30% for neuropathic pain; Likert 5-pt: -2.0 or -33% change; VAS 10-17mm improvement;			
VAS	NR	NR	✓
Likert scale	✓ 11-pt	✓ 4-pt	NR
Diff bet. Groups	No difference	Difference	No difference
Claim (trial)	Non-inferior	Superior	Non-inferior, post-hoc analysis
Claim (submission)	Non-inferior		
Pain relief: MCID: VAS or Likert scale: 25-30% improvement is clinically meaningful.			
Likert scale	NR	✓ 5-pt	✓ 5-pt
Diff bet. Groups	-	Difference	No difference
Claim (trial)	-	Superior	Non-inferior
Claim (submission)	Non-inferior		
Treatment satisfaction and patient overall assessment of study medication: NI margin, 4-pt scale: 20% improvement			
Likert scale	✓ 4-pt	✓ 5-pt	✓ 4-pt
Diff bet. Groups	No difference	Difference	No difference
Claim (trial)	Non-inferior	Superior	Non-inferior, post-hoc analysis
Claim (submission)	Non-inferior		

Source: Table 2.5.1, Table 2.5.2, Table 2.5.4 of the Commentary.

Abbreviations: diff = difference; MCID= minimum clinically important difference; NR = not reported; pt= point; VAS= visual analogue scale.

Chronic pain

- 6.16 The submission claimed that there were no differences in the outcomes of treatment satisfaction, overall assessment of study medication, and change in pain intensity, and improved pain relief with the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR groups in the treatment of chronic pain. The PSCR limited the restriction to acute pain, however ESC considered that there is a high risk of leakage to chronic pain and therefore issues related to chronic pain may still be relevant.
- 6.17 There were no significant differences between the FDC of tramadol 37.5 mg/paracetamol and tramadol 50 mg IR in the indirect comparison in the patients' overall assessment of study medication, however there were significant levels of heterogeneity seen in the meta-analysis.

Table 8: Patient overall assessment of study medication across the chronic pain trials

Comparison	Trial ID	T37.5+P325 or T50 n/N (%)	Comparator: placebo n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
T37.5+P325 vs PBO	CAPSS-104 ^a	74/162 (46)	56/159 (35)	10.5% (-0.2%, 21.1%)	1.30 (0.99, 1.70)	NR ^b
	CAPSS-112 ^a	91/161 (57)	52/157 (33)	23.4% (12.8%, 34.0%)	1.71 (1.32, 2.21)	NR ^b
	TRP-CAN-1 ^a	105/167 (63)	41/169 (24)	38.6% (28.8%, 48.4%)	2.59 (1.94, 3.47)	NR ^b
	CAPSS-114 ^a	101/153 (66)	82/153 (54)	12.4% (1.5%, 23.3%)	1.23 (1.02, 1.48)	NR ^b
	Meta-analysis: CAPSS-104, CAPSS-112, TRP-CAN-1 Test of heterogeneity				24.3% (8.1%, 40.5%) p=0.003 Q(df=2) = 14.7, p = 0.001 I ² =86.4%;	1.78 (1.22, 2.62) p=0.003 Q(df=2) = 11.8, p = 0.003 I ² =83%;
T50 vs PBO	CAPSS-051 ^a	63/28 (44)	66/18 (27)	17.2% (0.9%, 33.5%)	1.63 (1.01, 2.64)	NR ^b
T37.5+P325 vs T50	Indirect estimate of effect adjusted for the common reference (T37.5+P325 minus T50) Test of heterogeneity			7.1% (-27.6%, 41.8%) p=0.689 Q(df=2) = 14.7, p = 0.001 I ² =86.4%	1.09 (0.46, 2.59) p=0.837 Q(df=2) = 11.8, p = 0.003 I ² =83%;	1.30 (0.29, 5.83) p=0.733 Q(df=2) = 13.7, p = 0.001 I ² =85.4%

Source: Table 2-66 p171, Table 2-65 p 170, Table 2-67 p171 of the submission; CAPSS-114 CSR Table 9 p73; Attachment 3 p52 of the submission.

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group; NR= not reported; OR= odds ratio; PBO= placebo; RD= risk difference; RR= risk ratio;

Notes: a Assessed on a 5-point rating scale (very good = 2, good = 1, no change = 0, poor = -1, very poor = -2, with a positive response equivalent to good or very good pain control.); b Not reported in the submission and values were not calculated during the evaluation.

6.18 The submission claimed that in comparison to placebo, the FDC of tramadol 37.5 mg/paracetamol significantly reduced pain intensity by 10% based on the 100 mm visual analogue scale (VAS), and tramadol 50 mg IR reduced pain intensity by 12% based on the 5-point Likert scale, suggesting similar levels of improvement in pain intensity. The results of the meta-analysis included CAPSS-114, where a Cox-2 inhibitor was given concomitantly in both treatment groups.

Table 9: Results of the meta-analyses for change from baseline in pain intensity

Trials included in meta-analysis	Mean diff, FDC T37.5/P325 or T50 minus PBO) (95% CI)
Meta-analysis: pooled FDC T37.5/P325: 100 mm VAS CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114	Q(df=5) = 8.1, I ² =38.3%; p = 0.151 -10.38 (-13.68, -7.07) p<0.0001
Meta-analysis: Pooled T50: 5-pt Likert CAPSS-051, CA-R0027s	Q(df=1) = 3.1, I ² =67.6%; p=0.079 -0.61 (-1.02, -0.20) p=0.003

Source: Table 2-70 p176 and Table 2-71 p176, Attachment 3 Table 4 p12 and p45 of the submission;

Abbreviations: CI = confidence interval; FDC= fixed dose combination; LSM = least square mean; n = number of participants with event; NR= not reported; SE = standard error; **bold** = statistically significant; VAS= visual analogue scale

Notes: a CAPSS-051 and CA-R0027: 5-point Likert pain intensity scale (none=0, mild=1, moderate=2, severe=3, and extreme=4). The mean change in from baseline for each treatment arm was not reported. The results for individual studies were presented in the submission in Table 2-72 p178 and Table 2-73 p178 of the submission.

6.19 The submission claimed that a small, non-statistically significant difference was observed between the FDC of tramadol 37.5 mg/paracetamol and tramadol 50 mg IR in the indirect comparison (-0.50, 95% CI -1.4, 0.41). The submission claimed that based on the non-inferiority margin of 25-30%, the lower 95% CI of -1.4 represented approximately a 23% difference on a 6-point scale. There were significant levels of heterogeneity observed in the meta-analysis. There was a large numerical variation in the results for the individual trials.

Table 10: Results of the indirect comparison for pain relief

Trial	End of study, in pain relief using 6-point Likert scale; Mean (SD)			Mean difference (95% CI)
	FDC T37.5/P325	Common reference placebo	T50	
CAPSS-104	n=155 1.5 (1.36)	n=156 1.2 (1.49)	-	0.3 (-0.02, 0.62)
CAPSS-112	n=161 1.8 (1.34)	n=157 1 (1.28)	-	0.8 (0.51, 1.09)
CAPSS-113	n=156 1.6 (1.4)	n= 157 0.8 (1.33)	-	0.8 (0.5, 1.1)
TRP-CAN-1	n=167 1.8 (1.41)	n=169 0.6 (1.29)	-	1.2 (0.91, 1.49)
CAPSS-114	n=151 2 (1.18)	n=151 1.6 (1.21)	-	0.4 (0.13, 0.37)
pooled FDC T37.5/P325 Q(df=4) = 23.2, I ² =82.8%; p<0.001				0.70 (0.39, 1.02)
CAPSS-051	-	n=64 0.9 (SE 0.2)	n=63 2.1 (SE 0.2)	NR
Indirect WMD (95% CI) Q(df=4) = 23.2, I ² =82.8%; p < 0.001,				-0.50 (-1.4, 0.41)

Source: Table 2-62 p169, Table 2-63 p169, Table 2-64 p170, and Attachment 3 p45 of the submission.

Abbreviations: Abbreviations: CI = confidence interval; FDC= fixed dose combination; NR= not reported; SD= standard deviation; **bold** = statistically significant

Pain relief measured using a 6-point Likert scale (complete = 4, a lot = 3, moderate = 2, slight = 1, none = 0, worse = -1).

6.20 An overview of the results presented in the trials in chronic pain is presented in Table 11.

Table 11 Outcomes reported across the chronic pain trials

	Chronic Pain								
	T37.5+P325 vs PBO							T50 vs PBO	
	CAPSS-104	CAPSS-112	CAPSS-113	TRP-CAN-1	CAPSS-237	CAPSS-114	Chang 2013	CAPSS-051	CA-R0027
Pain intensity MCID: VAS: 10-17mm improvement; Likert 5-pt: -2.0 or -33% change									
VAS	✓	✓	✓	✓	✓	✓	NR	NR	NR
Likert scale	NR	NR	NR	NR	NR ^a	NR	NR	✓ 5-pt	✓ 5-pt
Diff bet. groups	No diff.	Diff	Diff	Diff	Diff	Diff	-	No diff.	Diff
Meta-analysis	Difference							Difference	
ITC	NR: Outcomes across trials were different.								
Claim (submission)	Non-inferior								
Pain relief MCID: VAS or likert scale: 25-30% improvement is clinically meaningful.									

	Chronic Pain								
	T37.5+P325 vs PBO							T50 vs PBO	
	CAPSS-104	CAPSS-112	CAPSS-113	TRP-CAN-1	CAPSS-237	CAPSS-114	Chang 2013	CAPSS-051	CA-R0027
Likert scale	✓ 6-pt	✓ 6-pt	✓ 6-pt	✓ 6-pt	NR ^a	✓ 6-pt	NR	✓ 7-pt	✓ 6-pt
Diff bet. groups	No diff.	Diff.	Diff.	Diff.	-	Diff.		Diff.	Diff.
Meta-analysis	Difference							NA [CA-R0027]	
ITC	No difference								
Claim (submission)	Non-inferior								
Patient overall assessment of study medication: MCID: Global rating of change: >1.35 point; Change of 28-30% is clinically meaningful.									
Likert scale	✓ 5-pt	✓ 5-pt	NR	✓ 5-pt	NR ^b	✓ 5-pt	NR	✓ 5-pt	NR
Diff bet. groups	Not diff.	Diff	-	Diff	-	Diff	-	Diff	-
Meta-analysis	Difference							NA	
ITC	No difference								
Claim	Non-inferior								
Quality of life and other scores; SF-36: bodily pain up to 20.35, physical function up to 20.4, physical component scale up to 4.8; WOMAC max values: physical function -2.65 to -2.60, pain -2.99, stiffness -2.59, global measure -1.47									
WOMAC: Index total score, Physical function, Pain, Stiffness [consistent across all domains]									
WOMAC	✓	NR	NR	NR	NR	✓	NR	✓	NR
Diff bet. groups	No diff.	-	-	-	-	No diff.	-	No diff.	-
Meta-analysis	No difference							No difference	
ITC	No difference								
Claim	Non-inferior								
SF-36	✓	✓	✓	✓	✓	✓	✓	NR	NR
Bodily pain	No diff.	Diff	Diff	Diff	Diff	Not diff.	NR	-	-
Meta-analysis	Difference							NA	
Physical function	No diff.	No diff.	Diff	Diff	Not diff.	Not diff.	Not diff.	NR	NR
Meta-analysis	Difference							NA	
Physical component	No diff.	No diff.	Diff	Diff	No diff.	Not diff.	NR	NR	NR
Meta-analysis	Difference							NA	

Source: Table 2.5.5, Table 2.5.6, Table 2.5.7, Table 2.5.11, Table 2.6.2, Table 2.6.3, Table 2.6.4, Table 2.6.5 of the Commentary.

Notes: a Part of BPI survey; b Likert scale 9-point;

Abbreviations: BPI= brief pain inventory; diff = difference in favour of the intervention group; ITC = indirect treatment comparison; MCID= minimum clinically important difference MOS = general health survey; NA = not applicable; NR = not reported; PBO= placebo; pt= point; SF-36 = short-form 36; VAS= visual analogue scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index.

6.21 The quality of life and other patient questionnaire results for the comparisons presented in the chronic pain setting are summarised as follows:

- Generally, statistically significant improvements were observed with the FDC when compared with placebo with most of the SF-36 domains, including the physical functioning, role-physical, bodily pain (except in CAPSS-114), vitality, social functioning, health transition scale and physical component summaries

(all $p < 0.05$). There were no statistically significant changes in the SF-36 in CAPSS-104 or Chang et al 2013.

- The MOS 6 item survey was used in CA-R0027 to measure QoL. Physical functioning, pain and social functioning were found to be statistically superior in the tramadol 50 mg IR compared with placebo.
- In the indirect comparison, the mean differences between treatments in final WOMAC total score, (0.59, 95% CI -0.27 to 1.45), amount of pain (0.53, 95% CI -0.37 to 1.43), or physical function (0.4, 95% CI -0.47 to 1.28) were not statistically significant. Based on the non-inferiority margins proposed; (upper 95% CI) pain 2.99, physical function 2.60, joint stiffness 2.08, and total score 1.47), the submission claimed that the FDC of tramadol 37.5/paracetamol 325 mg was non-inferior to tramadol 50 mg IR.

Comparative harms

Acute pain

6.22 Based on the pooled incidence of AEs from the trials of acute pain (ZAL-06, CAPSS-241 and GRTF-ZAL 1), the submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was superior in safety to tramadol 50 mg IR. The claim of superiority was adequately supported over a ten-day time horizon and appeared to be dose-related. This can be observed in the summary of key AEs presented in Table 12. Applicability of this finding to the clinical context in which tramadol 50mg is also used with paracetamol is not clear, as this is likely to result in less tramadol use and less dose related adverse effects in the tramadol 50 group.

Table 12: Summary of key AEs in the acute pain trials

Trial ID	T37.5+P325 n with event/N (%)	T50 n with event/N (%)	RD (95% CI)	RR (95% CI)
All AEs				
ZAL-06 (Day 2) ^a	54 (40.9)	74/129 (57.4)	-16.5% (-27.9%, -4.3%)	0.71 (0.55, 0.92)
CAPSS-241 (6 hours)	82/153 (53.6)	97/152 (63.8)	-10.2% (-20.9%, 0.8%)	0.84 (0.70, 1.02)
GRTF-ZAL 1 (10 days) ^c	30/59 (50.8)	44/60 (73.3)	-22.5% (-38.1%, -5.1%)	0.69 (0.52, 0.93)
Pooled	166/344 (48.3)	215/341 (63.0)	-14.8% (-22%, -7.4%)	0.77 (0.69, 0.88)
Nausea				
ZAL-06 (Day 2) ^a	34/132 (25.8)	47/129 (36.4)	-10.7% (-21.6%, 0.5%)	0.71 (0.49, 1.02)
CAPSS-241 (6 hours)	22/153 (14.4)	29/152 (19.1)	-4.7% (-13.1%, 3.7%)	0.75 (0.45, 1.25)
GRTF-ZAL 1 (10 days) ^c	8/59 (13.6)	21/60 (35)	-21.4% (-35.7%, -6.0%)	0.39 (0.19, 0.80)
Pooled	64/344 (18.6)	97/341 (28.4)	-9.8% (-16.1%, -3.5%)	0.65 (0.50, 0.86)

Source: Table 2-59 p160 and Table 2-60 p161 of the submission.

Abbreviations: AE= adverse events; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = risk ratio.

Chronic pain

6.23 Based on the results of the indirect comparison of the trials in chronic pain (CAPSS-104, CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013, CAPSS-051, CA-R0027) there were no differences in patients discontinuing for any reason,

discontinuations due to lack of efficacy, or due to AEs with the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR. There was a statistically significantly reduced risk of headache (RD -8.9%; 95% CI -14.8%, -2.9%), nausea (RD -11.7%; 95% CI -19.4%, -4%), constipation (RD -11.6%; 95% CI -18.7%, -4.6%) and pruritus (RD -5.9%; 95% CI -10.7%, -1.0%) with the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR. There was a numerical difference in the occurrence of treatment-related AEs, in favour of the FDC, but this did not achieve statistical significance.

Benefits/harms

- 6.24 As the submission claimed superior safety over its comparator, a summary of the comparative harms for the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR in acute pain is provided in Table 12. The data has limited applicability to practice where tramadol 50 mg IR should also be used in combination with paracetamol, with likely implications for efficacy, overall tramadol utilization and safety due to dose related adverse drug events. The clinical claim for efficacy was one of non-inferiority, thus an assessment of comparative benefits has not been presented.
- 6.25 On the basis of evidence presented in the submission, for every 100 patients with acute pain treated with the FDC of tramadol 37.5 mg/paracetamol 325 mg compared with tramadol 50 mg IR:
- Approximately ten fewer patients would experience nausea.

Clinical claim

- 6.26 The submission described the FDC of tramadol 37.5 mg/paracetamol 325 mg as non-inferior in efficacy and superior in safety compared with tramadol 50 mg IR in acute and chronic pain.
- 6.27 The efficacy and safety claims were not adequately supported for the treatment of acute pain when comparing the FDC of tramadol 37.5 mg/paracetamol 325 mg with tramadol 50 mg IR due to the heterogeneity of the trials and the limited applicability of the comparator to clinical practice. Furthermore, the appropriate comparator in clinical practice is tramadol IR 50 mg plus paracetamol 500 mg, which would have implications for efficacy and safety. Moreover, if the FDC is used in practice as a treatment for chronic pain, as originally proposed by the sponsor, the efficacy and safety beyond the titration phase are subject to a higher level of uncertainty. Differences between the trials, mainly pertaining to study design characteristics and placebo response rates, limited the transitivity of the trial results. Further, no evidence comparing the FDC with tramadol SR formulations was presented in the submission.
- 6.28 The submission stated that there is an unmet clinical need for an analgesic combination that will deliver a safer and efficacious outcome to patients, and an FDC

that is less likely to be abused. Although the submission presented a general discussion about the abuse potential associated with tramadol compared with other opioids, it was unclear about how substitution of one formulation of tramadol (50 mg IR) with another (the FDC) would meet the need for an analgesic that is less likely to be abused. The ESC noted that this has not been addressed and was additionally concerned that if this formulation is abused there is an additional risk of paracetamol toxicity.

- 6.29 The PBAC considered that the claim of non-inferior comparative effectiveness in acute pain was not adequately supported by the data due to the bias and heterogeneity of the trials and the limited applicability of the comparator to clinical practice.
- 6.30 The submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was superior in safety to tramadol 50 mg IR. The PBAC considered that the claim of superior safety may be reasonable over a ten-day time horizon based on the trial results, but was not adequately supported beyond 10 days.
- 6.31 The PBAC noted that since the appropriate comparator (in clinical practice) would be tramadol IR 50 mg plus paracetamol 500 mg, the efficacy and safety comparisons in practice would differ from the comparisons presented in the submission.

Economic analysis

- 6.32 The equi-effective doses were estimated in the submission as one tablet of the FDC of tramadol 37.5 mg/paracetamol 325 mg for one tablet of tramadol 50 mg IR. This estimation was based on the three direct randomised trials in acute pain: ZAL-06 (2 days); CAPSS-241 (6-hour); GRTF-ZAL 1 (10 days). The submission did not estimate an equi-effective dose of the FDC compared with any of the paracetamol/codeine formulations available on the PBS. The submission did not estimate an equi-effective dose of FDC compared to tramadol plus paracetamol given concomitantly which the ESC advised is the appropriate comparator in clinical practice.
- 6.33 The submission did not use the trials in chronic pain presented in Section 2 of the submission (CAPSS-112, CAPSS-113, TRP-CAN-1, CAPSS-237, CAPSS-114, Chang 2013, CAPSS-051, CA-R0027) to inform its economic analysis. This was inappropriate since the submission anticipated that the bulk of use of the FDC would be in the chronic pain setting. Estimates of drug dose and duration in chronic pain were based on additional studies from the literature (Meijjad et al. 2011 and Serrie et al. 2009) where the duration of treatment was one month. These provided limited data with which to conduct a robust comparison of treatment with the FDC of tramadol 37.5 mg/paracetamol 325 mg and tramadol 50 mg IR in chronic pain. The PSCR limited the restriction to acute pain, however the ESC considered that there is a high risk of leakage to chronic pain and therefore this issue may still be relevant.
- 6.34 The submission considered that cost offsets from reduced use of tramadol 50 mg IR would arise due to a lower incidence of constipation, which is based on results from

the indirect treatment comparison. The submission claimed that the incidence of constipation as an AE would be substantially reduced with the availability of the FDC. The submission estimated that the number of GP visits and pharmaceutical treatments to treat a patient with constipation would reduce by \$3.26 per patient in acute pain and \$23.44 in chronic pain. The ESC questioned the assumption that patients with constipation would require a GP visit. The PBAC considered that these cost offsets are unlikely to be realised, particularly in the acute pain setting.

- 6.35 The submission considered the potential for cost-offsets associated with the requirement for rescue medication with the use of paracetamol/codeine. The submission estimated cost-reductions of \$5.72 in acute pain and \$4.45 in chronic pain associated with a reduced need for rescue medications due to the use of the FDC of tramadol 37.5 mg/paracetamol 325 mg. The ESC questioned the assumption that patients requiring rescue medication would require a GP visit. The submission has not provided a clinical evaluation comparing the FDC of tramadol 37.5 mg/paracetamol 325 mg with paracetamol 500 mg/codeine 30 mg that allows validation of the claim with respect to the need for less rescue medication.
- 6.36 The submission's assumption of requiring additional rescue medication was based on a RCT of patients undergoing different day surgeries in Italy over two days. As it is proposed that treatments are used over a longer time horizon for chronic pain, extrapolation of the costs of additional rescue medication from a two-day study to use in chronic pain biased the cost-consequence analysis in favour of the FDC of tramadol 37.5 mg/paracetamol 325 mg.
- 6.37 A summary of dosages based on the PIs and costs of each treatment is presented in Table 13. The costs of the FDC of tramadol 37.5 mg/paracetamol 325 mg are higher than the costs of the higher strengths (above 50 mg) of the extended release formulation of tramadol; the SR formulation of tramadol is the only formulation PBS listed for ongoing use in chronic pain and therefore is more likely to be used for chronic pain than the IR form.

Table 13: Results of the cost-minimisation analysis

Formulation	Pack size (tablets)	Dosage for adult			AEMP		AEMP per day		
		Max daily	Initial	Dose interval	per tablet	per pack	Min	Max	Usual dose
Tramadol									
T 37.5 mg+ P 325 mg	20	8 tablets	2 tablets	Not less than 6 h PRN	\$0.093	\$1.86	\$0.093	\$0.744	\$0.372 to
	50	8 tablets	2 tablets		\$0.093	\$4.65	\$0.093	\$0.744	\$0.465 (4-5 tabs)
T 50 mg IR	20	8 tablets	1 to 2 tablets	Every 4 to 6 hours PRN	\$0.093	\$1.86	\$0.093	\$0.744	\$0.372 to \$0.465 (4-5 tabs)
T 50 mg SR	20	8 tablets	100m g QD	Usual dose: 200 mg QD, nocte	\$0.1465	\$2.93	\$0.293	\$1.172	\$0.586 (4 tabs)
T 100 mg SR	20	4 tablets			\$0.112	\$2.24	\$0.112	\$0.448	\$0.224 (2 tabs)
T 150 mg SR	20	400 mg ^a			\$0.15	\$3.00	\$0.15	\$0.30	\$0.30 (2 tabs)
T 200 mg SR	20	2 tablets			\$0.183	\$3.66	\$0.183	\$0.366	\$0.183 (1 tab)
Paracetamol and codeine									
P 500 mg C 30 mg	20	8 tablets	1 to 2	Every 4 hours PRN	\$0.063	\$1.26	\$0.063	\$0.504	NA

Source: URL: <http://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price> : Ex-manufacturer prices-non-efc-2017-12-01.xls.

TGA approved PI for each treatment.

Note: a the TGA approved PI for all strengths denoted 400 mg is the maximum daily dose of tramadol SR.

Abbreviations: AEMP = approved ex-manufacturer price; BID= twice daily; PRN= when necessary; QD= once daily; SR = sustained release.

Drug cost/patient/course

6.38 Using the published price requested in the submission, the cost per pack of a 20-tablet pack of the FDC of tramadol 37.5 mg/paracetamol 325 mg is \$13.09, and a 50-tablet pack is \$16.09. The drug cost for a course of treatment is estimated to be \$13.09 for acute pain assuming one pack of 20 tablets per patient is taken and, is \$32.18 for the treatment of chronic pain assuming two packs of 50 tablets per patient. The cost of treating chronic pain may be underestimated. At the maximum daily dose of 8 tablets, 100 tablets would provide sufficient drug for 12.5 days of treatment.

Estimated PBS usage & financial implications

6.39 This submission was considered by DUSC.

6.40 The submission adopted a market share approach in estimating the potential utilisation of the FDC of tramadol 37.5 mg/paracetamol 325 mg on the PBS, assuming substitution from tramadol 50 mg IR and paracetamol 500 mg/codeine 30 mg . A summary of the estimated use and financial implications for listing the FDC of tramadol 37.5 mg/paracetamol 325 mg for the treatment of acute and chronic

pain to the PBS is presented in Table 15. The proposed listing for use in chronic pain is broader than the current PBS listing for tramadol 50 mg IR, which is only listed for titration.

- 6.41 The estimated financial implications presented assumed that the FDC of tramadol 37.5 mg/paracetamol 325 mg would only substitute for current use of the 50 mg IR presentation of tramadol (restricted to acute pain and titration in chronic pain). This is not consistent with the proposed listing which would allow for use beyond titration in chronic pain and therefore would result in substitution of the FDC for other products in that setting, including higher dose strengths of the SR formulations of tramadol. Substitution of the FDC for higher strengths of SR formulations of tramadol would be likely to negate any cost savings estimated by the submission given that tramadol SR is administered less frequently, and the AEMP per dose is lower for tramadol SR \geq 100 mg than for the tramadol FDC.
- 6.42 As the financial estimates presented did not consider this difference in the circumstances of use, and other treatments listed on the PBS for chronic pain, such as substitution with the tramadol SR formulations, it is possible that the costs to the PBS may be higher than estimated in the submission.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a						
Estimated financial implications of the FDC of tramadol 37.5 mg/paracetamol 325 mg						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Estimated financial implications for Tramadol 50 mg IR, FDC paracetamol/codeine						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to Government (PBS/RPBS/MBS)	-\$	-\$	-\$	-\$	-\$	-\$

^a Assuming number of scripts dispensed as estimated by the submission.

Source: Table 4-9 p253, Table 4-10 p255, Table 4-12 p257, Table 4-13 p260 of the submission;

Note: ^a Figures in base case have been updated with changes to cells specified in Table 4.1.1 of the Commentary.

The redacted table shows that at year 6, the estimated number of scripts was 100,000 - 200,000 and the net saving to the PBS would be less than \$10 million.

- 6.43 The submission assumed that there was substitution of one pack of the FDC for every two of the nominated comparator. This was the key driver of the estimated

cost-savings to the PBS. When script substitution is assumed to be one to one, the cost to the PBS increased from \$ [REDACTED] in Year 1 to \$ [REDACTED] in Year 6. Similarly, when the extent of substitution for the FDC of paracetamol/codeine was increased (assumed to be [REDACTED]% in the base case), the savings to the PBS/RPBS were reduced.

- 6.44 The DUSC considered the estimates presented in the submission to be uncertain. The main issues were:
- There is a high risk of use beyond the restriction in chronic pain.
 - Given the unknown impact that up-scheduling of codeine will have on the prescription analgesic market, the DUSC considered that a market share approach has inherent uncertainty.
 - The submission assumed that there was substitution of one pack of the FDC for every two of the nominated comparator in chronic pain. As this substitution ratio is not applicable in the acute pain situation, the estimates changed from a net save to a net cost.
 - The offsets claimed from a lower incidence of constipation and need for rescue medication, are not likely to be realised in acute pain.

Quality Use of Medicines

- 6.45 No quality use of medicines information was provided in the submission. The submission did not assess the potential for abuse of the FDC compared with other formulations of tramadol available on the PBS, other than to state that there was less abuse potential associated with the FDC. The PSCR contended that due to the lower dosage of each component being dispensed in the FDC, additional QUM issues would not arise. The PSCR further stated that overuse of paracetamol would potentially decrease. The possible changes, such as reduced or increased opioid abuse if the FDC is listed on the PBS are unknown and not well described in the PSCR. The ESC was concerned of the risk of additional paracetamol toxicity if the FDC was abused. The PBAC agreed with ESC advice that the claim that there is less abuse potential associated with the FDC was not well-supported.
- 6.46 The submission did not present a QUM management plan on educating patients and providers on appropriate treatment of acute and chronic pain. The dosages administered to patients for the treatment of pain are variable, as the PIs recommend drug administration to be taken as needed. The ESC advised that a QUM management plan would be required and that it should also address the challenges of using multiple paracetamol containing formulations. The Pre-PBAC response noted that a number of activities will be undertaken by the sponsor to promote appropriate use and reduced misuse of the proposed FDC.
- 6.47 The submission has not discussed the QUM issues that arise from unused packs retained by patients following a course of treatment.
- 6.48 The ESC advised that the risk of accidental paracetamol overdose from use of

multiple paracetamol-containing formulations, including 'Zaldiar', an unfamiliar FDC containing an atypical dose of paracetamol for the Australian market, needed to be considered. The pre-PBAC response noted that all products containing paracetamol have labelling and dispensing software alerts to raise awareness of the risk of taking additional paracetamol.

- 6.49 The ESC advised that there is significant risk of underutilisation of paracetamol through the FDC with low dose paracetamol, impacting on analgesia and on requirements for tramadol. The pre-PBAC response disagreed that paracetamol may be underutilised with the low dose of paracetamol in the FDC and argued that it is a clinically appropriate amount.
- 6.50 The DUSC considered there to be a risk of misuse given current patterns and evidence of codeine and tramadol abuse. The DUSC also considered there to be a risk of adverse drug-related events that weren't addressed in the submission, including overdosing on FDC components and drug-drug interactions
- 6.51 There is a significant risk of leakage from the acute to the chronic pain setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the fixed dose combination (FDC) of tramadol hydrochloride 37.5 mg with paracetamol 325 mg for patients with acute pain on the basis of extensive quality use of medicines problems, questionable clinical place for the FDC, an inappropriate nominated comparator, and inadequately supported efficacy and safety compared with the relevant comparator. The PBAC considered that there were significant quality use of medicines issues associated with dosing with the FDC and the potential for abuse. The PBAC considered that the nominated comparator (treatment likely to be replaced in practice) was not appropriate, and that comparative efficacy and safety against the appropriate comparator had therefore not been established. The PBAC considered that the savings claimed due to reduced adverse effects and GP visits were not well supported and are unlikely to be realised in practice.
- 7.2 The PBAC noted that the proposed restriction was changed by the sponsor during the evaluation process to be limited to acute pain and the Committee agreed with the ESC that there is high potential for leakage to chronic pain, where the doses in the proposed FDC are unlikely to be appropriate. The PBAC also noted that the DUSC considered that there is some variability in the definition of acute pain and the PBAC agreed with the DUSC that there is uncertainty surrounding the appropriate quantity and number of repeats for the proposed restriction.
- 7.3 The PBAC considered that the clinical place for the FDC of tramadol 37.5 mg/paracetamol 325 mg was questionable given the QUM issues identified, specifically; the lack of flexibility in FDC doses which makes moving on and off the

FDC difficult, the uncertain clinical appropriateness of the component doses and immediate release (IR) form of tramadol, and the potential for abuse or dosing errors.

- 7.4 The PBAC considered that the nominated comparator of 50 mg tramadol IR was not appropriate and does not represent best practice. The PBAC agreed with the ESC that the concomitant use of the components is the most appropriate comparator, particularly as use of tramadol 50 mg IR is recommended by national and international guidelines together with a step 1 analgesic such as paracetamol. The PBAC agreed with the ESC that the secondary comparator of the FDC of paracetamol 500 mg and codeine phosphate 30 mg was appropriate as it has a similar place in therapy. The PBAC also noted that no comparisons with higher doses or alternative formulations of tramadol were presented and considered that these could also be considered as relevant comparators.
- 7.5 The PBAC noted that the evidence for the comparison with tramadol 50 mg IR was based on three head-to-head trials comparing the FDC of tramadol 37.5 mg/paracetamol 325 mg to tramadol 50 mg IR for treatment of acute pain (ZAL-06, CAPSS-241, and GRTF-ZAL-1). The PBAC considered that there was risk of bias in the trials presented and heterogeneity among the trials, pertaining to the source of pain, the methods of pain management, differences in the non-inferiority margins applied and the concomitant medications used during the trials. The submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was non-inferior to tramadol 50 mg IR. However, the PBAC considered that the submission's claim of non-inferior efficacy was not adequately supported due to the heterogeneity in the trials and the limited applicability to clinical practice where tramadol 50 mg IR would be used in combination with paracetamol.
- 7.6 The submission claimed that the FDC of tramadol 37.5 mg/paracetamol 325 mg was superior in safety to tramadol 50 mg IR. The PBAC considered that the claim of superior safety may be reasonable over a ten-day time horizon based on the trial results, but was not adequately supported beyond 10 days.
- 7.7 The PBAC noted that since the appropriate comparator (in clinical practice) would be tramadol IR 50 mg plus paracetamol 500 mg, the efficacy and safety comparisons in practice would differ from the comparisons presented in the submission.
- 7.8 The PBAC noted that if used for chronic pain there is additional uncertainty in the comparative efficacy and safety of the FDC of tramadol 37.5 mg/paracetamol 325 mg.
- 7.9 The PBAC noted that the submission did not formally establish superiority of the FDC of tramadol 37.5 mg/paracetamol 325 mg over the secondary comparator paracetamol 500 mg/codeine 30 mg, relying instead on the existing therapeutic relativity sheets and the superiority of tramadol 50 mg IR over paracetamol 500 mg/codeine 30 mg. The PBAC considered that the superiority over the FDC paracetamol/codeine was not adequately supported.

- 7.10 The PBAC noted the submission presented a general discussion about the abuse potential associated with tramadol compared with other opioids, however the PBAC noted that no data was provided to support the assumption that substitution of one formulation of tramadol (50 mg IR) with another (the FDC) would meet the need for an analgesic that is less likely to be abused.
- 7.11 The PBAC noted that the proposed equi-effective doses were estimated as one tablet of the FDC of tramadol 37.5 mg/paracetamol 325 mg for one tablet of tramadol 50 mg IR, based on the trials presented in acute pain. However, the PBAC considered that this was not the appropriate comparator. The PBAC noted that the submission did not estimate an equi-effective dose of the FDC compared with any of the paracetamol/codeine formulations available on the PBS or for tramadol and paracetamol given concomitantly.
- 7.12 The PBAC noted that the costs for the FDC of tramadol/paracetamol were higher than the cost for higher strengths of tramadol and higher than the cost for the FDC paracetamol 500 mg/codeine 30 mg. The PBAC noted that the economic evaluation presented relied on cost offsets from a lower incidence of constipation and less need for rescue medication resulting in fewer GP visits and pharmaceutical treatments. The PBAC considered that these costs-offsets are unlikely to be relevant in the acute pain setting and would be unlikely to be realised because FDC paracetamol/codeine or concurrent tramadol and paracetamol are more likely to be substituted than tramadol 50 mg alone. The PBAC considered that for these comparators the equi-effective doses, reduction in AEs and requirements for rescue medication have not been established.
- 7.13 The PBAC agreed with the DUSC advice that the financial estimates presented were highly uncertain due to the high risk of use beyond the restriction in chronic pain and uncertainty in the market share approach, as it is unknown what impact the up-scheduling of codeine will have on the prescription analgesic market. In addition, the PBAC noted that the submission assumed there would be substitution of one pack of the FDC for every two of the nominated comparator. The PBAC agreed with the DUSC that this substitution ratio is not applicable in the acute pain setting, so it is likely there would be a net cost to the PBS associated with the proposed listing, rather than the net saving presented as the base case. The PBAC also considered that cost offsets in the financial estimates from reduced AEs and GP visits were not well supported in the clinical data presented and are unlikely to be realised in practice in the acute pain setting.
- 7.14 The PBAC noted that a number of substantial QUM issues were raised including the questionable clinical place for the FDC of tramadol 37.5 mg/paracetamol 325 mg, the potential for abuse, the risk of overdose or underutilisation of paracetamol, inappropriate conversion to chronic use, AEs and drug-drug interactions that were not addressed in the submission. Overall the PBAC did not accept that there is a clinical place for proposed drug on the PBS, and considered that the clinical claim, costs and offsets were not supported because the comparator presented was

inappropriate. The PBAC considered that it is unlikely that these issues could be adequately addressed in a resubmission.

7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Aspen continues to believe there is a clinical place for fixed dose combination analgesics for acute pain management, in particular Zaldiar. Zaldiar has proven efficacy and superior ADRs/AEs profile compared to tramadol 50mg IR capsules, which provides doctors with an option for acute pain management.