PTAC minutes are published in accordance with the following definitions from the PTAC Guidelines 2002:

“Minute" means that part of the record of a PTAC or Sub-committee meeting (including meetings by teleconference and recommendations made by other means of communication) that contains a recommendation to accept or decline an application for a new investment or a clinical proposal to widen access and related discussion.”

Note that this is not necessarily a complete record of the PTAC meeting; some material may be withheld for reasons such as protection of supplier commercial information that has been supplied in confidence.

Record of PTAC meeting held 21 & 22 February 2007

- Pegylated interferon with ribavirin for HCV genotypes 2 & 3 without cirrhosis
- Paclitaxel for second-line treatment of germ cell tumour of the testis
- Solifenacin (Vesicare) for overactive bladder
- Sibutramine hydrochloride (Reductil) for severe obesity
- Varenicline (Champix) for smoking cessation
- Buprenorphine/naloxone (Suboxone)
- Ondansetron and tropisetron for patients receiving radiation therapy
PTAC reviewed the record of the PTAC meeting held on 21 & 22 February 2007 and made the following minor amendments:

Rituximab (MabThera) – paragraph 10.10: replace “(QALY) gains was difficult” with “(QALY) gains difficult”.

Dipyridamole 200 mg modified release (Persantin), dipyridamole 200 mg modified release with 25 mg acetylsalicylic acid (Asasantin) and the dipyridamole Special Authority criteria – paragraph 14.4: replace “Committee also noted the results of other literature including” with “Committee also noted the other published trials including”

Methylphenidate long-acting (once-daily) formulation (Ritalin LA) – paragraph 16.5: replace

“16.5 The Committee considered that the patients who would most benefit from methylphenidate long-acting would be those for whom compliance with existing formulations was a problem and those for whom there was a significant risk of diversion associated with taking tablets to school for a midday dose. Members considered that, within this patient group, Maori and Pacific peoples could have a greater unmet need than the population as a whole.”

with

“16. 5 The Committee considered that the patients who would most benefit from methylphenidate long-acting would be those for whom compliance with existing formulations was a problem and those for whom there was a significant risk of diversion associated with taking tablets to school for a midday dose.

16.6 Members considered that Maori and Pacific peoples could have a greater unmet need than the population as a whole.”

Topiramate (Topimax) – paragraph 19.7: replace “patients who had failed” with “patients in whom funded alternatives had failed”

Sunitinib (Sutent) – paragraph 20.7: replace “interferon alfa” with “interferon alpha”.

Sunitinib (Sutent) – paragraph 20.13: replace “treatement” with “treatment”.

Sunitinib (Sutent) – paragraph 20.19: replace “limited it’s usefulness” with “limited its usefulness”.

Pegylated interferon with ribavirin for HCV genotypes 2 & 3 without cirrhosis

The Committee reviewed an application from clinicians on behalf of the New Zealand Society of Gastroenterology to widen access to pegylated interferon alpha 2a with ribavirin (Pegasys) for the treatment of patients with chronic hepatitis C genotype 2 and
3 without cirrhosis, with treatment limited to 24 weeks. The applicants considered that patients with chronic hepatitis C genotype 2 and 3 without cirrhosis represent about 10% of the hepatitis C patient population, approximately 40 patients per year.

The Committee noted that, at present, funding for pegylated interferon alpha 2a with ribavirin (Pegasys) and pegylated interferon alpha 2b with ribavirin (Pegatron) is limited to chronic hepatitis C, genotype 1, 4, 5 or 6 infection or HIV co-infection, or genotype 2 or 3 with bridging fibrosis or cirrhosis (Metavir stage 3 or 4 or equivalent) or patients unsuitable for liver biopsy due to coagulopathy.

The Committee noted that these patients currently have funded access to standard interferon therapy alpha 2a or 2b (with or without ribavirin). However, the Committee noted that a study by Fried et al (NEJM 2002;347:975-82) demonstrated that pegylated interferon alpha 2a with ribavirin significantly improved sustained viral response compared with standard interferon alpha 2b therapy with ribavirin (78% vs 61%) over 48 weeks.

The Committee noted that there was no data comparing 24 weeks pegylated interferon alpha 2a with ribavirin against 24 weeks standard interferon alpha with ribavirin, and noted that such a study would likely never be done.

The Committee considered that although the applicants requested that treatment be limited to 24 weeks it may be possible for some patients to stop treatment at 16 weeks for those with a rapid virological response; however, this would require four-weekly viral load testing.

The Committee noted guidance issued by the UK National Institute of Health and Clinical Excellence (NICE) in August 2006 that recommended the use of pegylated interferon alpha with ribavirin in patients with mild chronic hepatitis C. The Committee also noted a Canadian Agency for Drugs and Technology in Health (CADTH) technology assessment report on interferon (pegylated and non-pegylated) treatment for chronic hepatitis C.

The Committee considered that the treatment of hepatitis C genotype 2 and 3 without cirrhosis with pegylated interferon alpha 2a and ribavirin was associated with clinical benefit and noted that the NICE guidance considered that there was a reasonable cost per QALY.

The Committee recommended that access to pegylated interferon alpha 2a with ribavirin on the Pharmaceutical Schedule be widened to include treatment of hepatitis C genotype 2 and 3 without cirrhosis for up to 24 weeks. The Committee gave this recommendation a medium priority.

The Committee further recommended that the Special Authority criteria for pegylated interferon alpha 2a with ribavirin and pegylated interferon alpha 2b with ribavirin be amended to include a stopping rule for patients who fail to achieve virological response (at least a 2-log reduction) after 12 weeks of treatment. The Committee recommended that the application be reviewed by the anti-infective Sub-Committee for further advice regarding appropriate Special Authority criteria.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing
medicines, therapeutic medical devices and related products and related things; (iv) The
clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting
health needs by funding pharmaceuticals rather than using other publicly funded health
and disability support services.

Paclitaxel for second-line treatment of germ cell tumour of the testis

The Committee reviewed an application from [ ],[a clinician] to widen access to paclitaxel on the Pharmaceutical Schedule for the treatment of relapsed, or resistant, germ cell tumour of the testis in combination with other chemotherapy.

The Committee noted that germ cell tumours (GCTs) are a morphologically distinct group of neoplasms with varied clinical presentation. Ninety-five percent of tumours arising in the testes are GCTs, indicating that they originate from the primordial germ cells. Members further noted that 80-90% of patients with GCT diagnosed early are cured, with delays in diagnosis correlating with a higher stage at presentation and, consequently, a lower cure rate. The success in treating GCTs in the past two decades is attributed largely to the effectiveness of cisplatin-containing combination chemotherapy in curing advanced disease. However, about 20-30% of patients have a relapse or do not achieve a complete response to cisplatin-based chemotherapy.

The Committee noted that in New Zealand 124 cases of GCT were reported in 1996 with approximately 163 cases per year projected for 2011, therefore, the number of patients requiring second line treatment would likely be small, less than 20 per year.

The Committee reviewed three main studies, all of which were conducted by the Memorial Sloan-Kettering Cancer Institute. The first study (Motzer et al Journal of Clinical Oncology 2000: Vol 18 (Jun); 2413-2418) was a phase I/II study in 30 relapsed GCT patients with favourable prognostic factors. Patients were treated with four cycles of combination paclitaxel, ifosfamide and cisplatin (TIP), the dose of paclitaxel was increased in cohorts from 175 to 250 mg/m². Members noted a complete response rate of 77% after 33 months follow-up, which compares favourably with 36-50% response rate in historical controls.

In the other two studies (Motzer et al Journal of Clinical Oncology 2000: Vol 18 (Mar); 1173-1180 and Varuni Kondagunta et al Journal of Clinical Oncology 2007: Vol 25 (Jan); 85 – 90) patients with relapsed GCTs and poor prognostic indicators were treated with high dose chemotherapy (2 cycles paclitaxel and ifosfamide, stem cell harvest, followed by 3 cycles carboplatin plus etoposide) followed by stem cell transplant (TICE). Members noted that these small phase II studies reported a complete response rate in the region of 50% with durable response out to 30 months in approximately 40% of patients. Again this compares favourably with 31% complete response rate and 15% durable response rate in historical controls.
The Committee considered that the quality of evidence was moderate to poor, but considered that in this relatively rare tumour type it was unlikely that any better data would be generated.

The Committee noted that paclitaxel is now available as a generic and that its price has been decreasing and is likely to decrease further. Members considered that there would likely not be a significant increase in expenditure if the Special Authority criteria were removed given that the current Special Authority criteria were extensive, covering most common usages for this pharmaceutical. Members recommended that the Special Authority criteria for paclitaxel be removed, allowing access for germ cell tumour of the testis. They gave this recommendation a high priority.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (viii) The Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere.

**Solifenacin (Vesicare) for overactive bladder**

The Committee considered an application from CSL Biotherapies for the listing of solifenacin (Vesicare) for the treatment of patients with overactive bladder.

The Committee noted that the evidence in support of the submission was based on an indirect comparison between solifenacin and oxybutynin by way of a series of comparisons to tolterodine immediate release and tolterodine extended release. Members noted that the supplier did not provide good evidence to substantiate all parts of this indirect comparison.

Members noted that the submission contained three well-conducted clinical trials - one comparing solifenacin with placebo, one comparing solifenacin with placebo and tolterodine immediate release; and one comparing solifenacin with tolterodine extended release. Solifenacin produced statistically significant, yet clinically modest, improvement compared with placebo and even more modest benefits compared with tolterodine.

The Committee noted that the supplier raised concerns over the effect that oxybutynin had on memory in elderly patients, but that there was no evidence in the submission either to support this concern or to show that this effect is less with solifenacin. The Committee considered that whilst indirect comparisons suggest that solifenacin has a better side-effect profile compared with oxybutynin, in the absence of a direct comparison, it is difficult to determine which product has a better side-effect profile. The Committee noted that, in the clinical trials, solifenacin was associated with an increased frequency of anticholinergic adverse effects compared with tolterodine. Members noted that there was insufficient evidence to determine whether solifenacin had any effect on falls or confusion.
The Committee noted that there is no alternative agent listed in the Pharmaceutical Schedule for patients with an intolerance of oxybutynin. Members noted that this patient group would potentially benefit most from the availability of solifenacin.

The Committee considered that if solifenacin was listed in the Pharmaceutical Schedule, it would have to be as a second-line therapy behind oxybutynin. However, members noted that it is difficult to accurately define intolerance to oxybutynin, and that adverse effects are common to both agents.

Members noted that the supplier’s estimates of the likely population treated with solifenacin were an underestimate relative to incidence rates and current oxybutynin prescription volumes, and accordingly the costs of listing solifenacin are likely to be higher than those estimated by the supplier.

The Committee recommended listing solifenacin in the Pharmaceutical Schedule, as a second-line agent for patients with a documented intolerance of oxybutynin, and gave this recommendation a low priority.

The decision criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand (as some patients are not being treated for overactive bladder due to intolerance to oxybutynin); (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things, (as many patients develop intolerance to oxybutynin); (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services (as the cost of solifenacin is very high relative to its benefit); (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule (as listing solifenacin would be likely to have a significant impact on pharmaceutical expenditure); and (vii) The direct cost to health service users (as some patients are currently self-funding alternative treatments for overactive bladder).

Sibutramine hydrochloride (Reductil) for severe obesity

The Committee considered an application for the funding of sibutramine hydrochloride (Reductil) from Abbott Laboratories for the treatment of severe obesity under the following Special Authority criteria:

**Initial Application** For the treatment, in conjunction with a reduced caloric diet, of severe obesity (BMI ≥ 35 kg/m²) in adults between 18 and 65 years of age who:

1. are normotensive with adequately controlled hypertension (< 145/90 mmHg) **AND**
2. have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) **AND**
3. have two or more of the following risk factors:
   3.1 Type 2 diabetes **OR**
   3.2 Triglycerides > 150 mg/dL (>1.695 mmol/L); **OR**
3.3 HDL < 50 mg/dL (<1.295 mmol/L) for females or < 40 mg/dL (<1.036 mmol/L) for males

**First Renewal**
1. Patient has been diagnosed with diabetes AND:
2. A weight review has been undertaken and shows a 5% reduction in initial bodyweight after six months of treatment OR
3. A weight review has been undertaken and shows a 5% reduction in initial bodyweight after three months of treatment

**Further Renewal**
Continuing treatment in patients who initially responded adequately to therapy as outlined above. Total treatment will not exceed 24 months from initial application.

The Committee considered that the application was of sufficient strength and quality; however, it considered that the quality of the application could have been improved by indexed references to the key studies.

The Committee noted that sibutramine did not have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule, and that if listed, it would create a new area of expenditure from the Pharmaceutical Budget.

The Committee noted the patient-level analysis of 23 trials. Data was analysed from a sub-group of patients from those trials (243 (7.4%) patients) who would be eligible for listing under proposed Special Authority criteria. The analysis indicated that 54% of sibutramine patients compared with 21.4% placebo patients would be likely to lose at least 5% of bodyweight.

The Committee noted that there was insufficient evidence to determine the long-term benefits and risks associated with treatment. Members considered that the hypertensive effects associated with initiation of treatment could negate the secondary antihypertensive effects associated with weight loss.

The Committee noted that in clinical trials the weight loss associated with sibutramine only persisted while patients were taking treatment. The Committee noted the results of the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) trial (Int J Obes Relat Metab Disord. 2001 Apr;25(4):496-501), where patients were treated for 24 months (providing they benefited from treatment at 6 months). Of the 204 sibutramine patients that completed the trial, 43% maintained 80% of the original weight loss, compared with 16% of patients in the placebo group. The Committee therefore questioned the practicality of restricting access to only two years for patients who may be benefiting from treatment. The Committee considered that if funding were approved, access would probably need to be made available for as long as patients are receiving therapeutic benefit from treatment. Members noted that if funding were approved for patients indefinitely, the cost would be substantially higher and hence the budget impact would be greater.

The Committee questioned whether a 5% weight loss was large enough to result in a substantial improvement in clinical outcomes or quality of life over an extended period of time. Members noted that unless significant and sustainable lifestyle changes were made in conjunction with rapid weight loss, rebound weight gain is likely to be associated with cessation of treatment. Members considered that there may be greater
benefits if treatment was targeted to more severely obese patients (BMI ≥ 40 kg/m²) in conjunction with targeted and intensive dietetic and physical support.

The Committee noted that a cost-utility analysis (CUA) had been provided by Abbott Laboratories. The Committee noted that the estimated cost per quality-adjusted life year (QALY) of sibutramine compared with lifestyle modification alone under the Special Authority criteria was $8,754. The Committee noted that PHARMAC staff had reviewed the analysis, and that the actual cost per QALY was likely to be higher than that estimated by the supplier. The Committee questioned whether surgical procedures such as gastric banding would be a more appropriate comparator, but noted that there are disparities in access to gastric procedures in New Zealand.

The Committee considered that there was not a clear link between results seen in the evidence provided and the proposed access criteria. The Committee recommended that the application be declined.

The Committee considered that while obesity should be treated as a chronic disease, treatment should target all causative factors. This includes changes not only in lifestyle but community/whanau attitudes.

The Decision Criteria relevant to this recommendation are: (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.

Varenicline (Champix) for smoking cessation

The Committee considered an application from Pfizer New Zealand for the listing of varenicline (Champix) as a smoking cessation treatment on the Pharmaceutical Schedule.

The Committee noted that the application was for a 12-week course in association with a counselling programme.

The Committee noted that nicotine replacement therapy (NRT) and nortriptyline are currently listed on the Pharmaceutical Schedule, bupropion is not listed, and that NRT is managed via Quitline. The Committee also noted that varenicline has a higher cost per day than the alternative treatments.

The Committee noted that a number of studies had directly compared varenicline with placebo and bupropion, but that none had directly compared varenicline with NRT or nortriptyline.

The Committee noted that varenicline reduces craving and withdrawal symptoms compared with placebo, and that it had higher rates of abstinence than bupropion and placebo. The Committee noted that the studies were performed in association with counselling and considered that the level of counselling in the studies was more than is
likely to be available to most people in New Zealand attempting to quit. The Committee considered that if varenicline were to be used then it should be used as part of a quitting/support program.

The Committee noted that a significant number of patients treated with varenicline experienced nausea, although it was mostly mild and reduced with time and dose titration. The Committee considered that, overall, varenicline was reasonably well tolerated although there were adverse effects including abnormal dreams, headaches and insomnia.

The Committee noted that there is no information regarding the safety and efficacy of varenicline in pregnancy or in Maori/Pacific Island populations.

The Committee considered that while the quality of the evidence supplied in the application was good, there were no direct head-to-head studies to provide evidence of treatment outcomes (quit rates) with varenicline compared with either NRT or nortriptyline.

The Committee noted that New Zealand is one of very few countries where nortriptyline is registered for smoking cessation. The Committee considered that a relatively high dose of nortriptyline was required and that many smokers would not be able to tolerate the recommended dose. The Committee considered that it was unlikely that nortriptyline would be widely used for smoking cessation and that it is unlikely that any studies would be done comparing varenicline to nortriptyline. The Committee, therefore, considered that nortriptyline may not necessarily be the most appropriate comparator for determining the cost-effectiveness of varenicline.

The Committee considered that NRT (with associated Quitline services) was the most appropriate comparator to use in the cost-utility analysis of varenicline, and noted that the supplier has indicated that studies comparing varenicline to NRT are pending. The Committee also noted that the NICE evaluation is pending.

The Committee noted the rapid analysis of the cost-effectiveness of varenicline compared with NRT and Quitline that was provided in the application. The Committee noted that indirect comparisons were used to derive the incremental benefit of varenicline over NRT, limited to short-term follow-up data, and that the results were not discounted. The Committee considered that formal cost-effectiveness analysis should be undertaken when the long-term follow-up results of the head-to-head trial become available.

The Committee therefore recommended that any decision on the funding or determining the cost-effectiveness of varenicline be deferred pending the outcome of head-to-head trials with NRT, and until longer-term data with regards to treatment efficacy and safety is available.

Buprenorphine/naloxone (Suboxone)
The Committee considered an update of a cost-utility analysis (CUA) in a Technology Assessment Report (TAR) provided by PHARMAC staff on Suboxone (buprenorphine with naloxone) for opiate dependence. Members noted that Suboxone had previously been considered by PTAC in August 2005, February 2006 and May 2006, and by the Mental Health Subcommittee of PTAC in October 2006. The Committee noted that, in May 2006, it had considered, and commented on, an earlier version of the CUA.

The Committee noted that two separate analyses had been undertaken, representing the different treatment programmes:– detoxification (complete withdrawal from illicit opioid use with no planned maintenance treatment) and maintenance treatment. The Committee noted that PHARMAC staff had made a number of amendments to the assumptions underpinning the CUA following receipt of further expert clinical advice, advice from the Mental Health Subcommittee of PTAC and information from the Ministry of Health and opioid addiction treatment centres.

The Committee considered that the amendments to the revised CUA were appropriate, and that overall the assumptions in the revised analysis were reasonable. Members noted that many of the assumptions were based on expert opinion; however, members considered that this was appropriate given the unique nature of opioid addiction treatment in New Zealand.

Members noted that the revised analysis indicated that Suboxone was cost-saving for use in detoxification from illicit opioid use. It was noted that the actual amount of savings to DHBs from detoxification is uncertain and could be nominal, depending on the number of patients currently on the waiting list and whether patients currently receiving Suboxone remain in hospital for the full detoxification period.

Members noted that at current prices the cost per quality-adjusted life year gained for the use of Suboxone in maintenance treatment of opioid addiction was relatively high compared with that of other pharmaceuticals under consideration for funding. The Committee noted that for Suboxone to be more cost-effective in maintenance treatment it would either need to be shown to be significantly more effective than methadone or the price of Suboxone would need to decrease.

After taking all the information (including that presented at previous meetings) into consideration, the Committee recommended listing Suboxone in the Pharmaceutical Schedule for use in recognised opioid addiction treatment centres: for detoxification with a high priority and in maintenance treatment with a low priority. Members considered that any decision to list Suboxone should be made in close consultation with the Ministry of Health.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (viii) The Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere.
Ondansetron and tropisetron for patients receiving radiation therapy

The Committee reviewed an application from a radiation oncologist to review the restrictions on the 5HT₃ antagonists ondansetron and tropisetron for patients receiving radiation treatment.

The Committee noted that the recommended regimen for ondansetron in preventing nausea and vomiting during standard regimens of highly emetogenic chemotherapy and/or radiation therapy is 8 mg 1–2 hours before treatment, continued for five days after treatment at a dose of 8 mg twice daily. The Committee noted that the recommended regimen for tropisetron in preventing nausea and vomiting during highly emetogenic chemotherapy is a six-day course of 5 mg per day. Members noted that current restrictions did not permit dispensing of the recommended regimen in a single dispensing.

The Committee noted that there were an increasing number of cancer treatments that involved prolonged emetogenic chemotherapy and/or radiation therapy, and that current restrictions prevented the optimal use of ondansetron or tropisetron in preventing nausea and vomiting in patients undergoing such treatments. Members noted that many patients were currently receiving prescriptions for both ondansetron and tropisetron in order to obtain larger quantities of 5HT₃ antagonists per month.

Members reviewed the supporting references provided, and noted that these were mostly in the form of reviews referring to studies performed some years ago, the largest of which was an observational study from the Italian Group for Anti-emetic Research in Radiotherapy (IGARR) published in 1999.

The Committee noted that the general consensus from both the Multinational Association of Supportive Care in Cancer (MASCC) and the American Society of Clinical Oncology (ASCO) is that 5HT₃ antagonists should be made available as both prophylactic and therapeutic agents for oncology patients at moderate or high risk of nausea and vomiting.

The Committee considered that any restrictions on the use of ondansetron and tropisetron would be based on financial, not clinical, considerations.

The Committee recommended waiving the restrictions on ondansetron and tropisetron for patients with cancer undergoing highly emetogenic chemotherapy and/or radiation therapy under the following proposed Special Authority criteria, with a high priority.

SAXXXX Special Authority for Waiver of Rule
Initial application from any relevant practitioner. Approvals valid for 12 months where patient is undergoing prolonged treatment with highly emetogenic chemotherapy and/or highly emetogenic radiation therapy for the treatment of malignancy.
Renewal from any relevant practitioner. Renewals valid for 12 months where patient is undergoing prolonged treatment with highly emetogenic chemotherapy and/or highly emetogenic radiation therapy for the treatment of malignancy.
The Committee considered that it would be sufficient to expand access to just one agent, preferably ondansetron.

The Committee considered that cases of hyperemesis gravidarum requiring ondansetron were being dealt with adequately under hospital exceptional circumstances.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (viii) The Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere.