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Department of Health and Ageing

Therapeutic Goods Administration

Guideline for Levels and Kinds of Evidence for Listed Medicines with Indications and Claims for Weight Loss

Consultation draft

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Guideline for Levels and Kinds of Evidence for Listed Medicines with Indications and Claims for Weight Loss

Contents

Introduction

There is no simple solution to losing weight. The three major components of managing weight loss involve dietary control, physical activity and behavioural change. Medicines should only be considered as an adjunct to these lifestyle components, and are not a "magic bullet" for losing weight. Claims should not arouse unwarranted and unrealistic expectations of the product's effectiveness in this regard. Despite years of research, a simple medicinal solution is still elusive. There are no effective long-term solutions that do not involve some form of lifestyle change.

This Guideline has been developed to assist sponsors of Listed complementary medicines in determining the level and kind of evidence to support indications and claims for weight loss. It should be applied as an addition to the *Guidelines for Levels and Kinds of Evidence to Support Indications and Claims for Non-Registerable Medicines, including Complementary Medicines and other Listable Medicines*[1] (the Guidelines).

This Guideline will also help ensure consistency in the type and level of evidence required to support indications and claims for weight loss in Listed medicines and give consumers confidence in the medicines they choose for self-care. In line with general principles for evaluating evidence, a framework for rating scientific evidence was adapted from the National Health and Medical Research Council's *Designation of Levels of Evidence.*

Weight Loss

Classification of Overweight & Obesity

Overweight and obesity are a continuum of increasing body weight due to excessive body fat. Various measures for estimating body fat are available. All are indirect and therefore subject to some uncertainty. At the clinical level, the most frequently used anthropometric measure of body mass is either weight or weight adjusted for height. Body mass index (BMI) is widely used as a measure to classify overweight and obesity and was introduced to correct for the inadequacies using weight alone. On a population basis, BMI correlates closely, but not perfectly, with body fat mass (see below).

This Guideline uses the graded Body Mass Index (BMI)[2] as a measure to classify overweight and obesity. BMI is believed to provide the most useful population-level measure of overweight and obesity[3]. BMI is calculated as the body weight (in kilograms) divided by the square of the height (in metres).

$$\textit{Body mass index}\ (\text{BMI}) = \frac{\textit{weight}\ (kg)}{\textit{height}\ (m)^2}$$

BMI values for the cut-off points for classification of overweight and obesity vary within different countries. According to the World Health Organization (WHO) Guidelines, a BMI of 18.5 to 24.9 kg/m2 is normal, 25 to 29.9 kg/m2 is classified as overweight or pre-obese, over 30 kg/m2 is classified as obese, which includes obese class I (30 to 34.9 kg/m2), obese class II (35 to

[1] Guidelines for Levels and Kinds of Evidence to Support Indications and Claims - http://www.tga.gov.au/docs/html/tgaccevi.htm
[2] Various measures for estimating body fat are available. All are indirect and therefore subject to some uncertainty. At the clinical level, the most frequently used anthropometric measure of body mass is either weight or weight adjusted for height.
[3] World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity. WHO Technical report series 894, Geneva: WHO 2000.

39.9 kg/m2) and obese class III (> 40.0 kg/m2). A BMI of less than 18.5 kg/m2 is classed as underweight (**Table 1**). This classification is based on standards for adults of European descent.[4]

Table 1 – Classification of Overweight and Obesity by BMI.[5]

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	>40.0

The relationship between BMI and body fat content varies somewhat with age, sex, and possibly ethnicity because of differences in factors such as composition of lean tissue, sitting height, different body proportions and hydration state.

The Use of Medicines in Weight Loss

Elevated BMI is associated with morbidity and mortality that increase successively for overweight and obese subgroups of the population. Being overweight does not necessarily incur a detrimental effect to health in a particular individual and medicines may be useful together with controlled energy intake and increased energy expenditure to assist with weight loss in individuals with elevated BMI. Listed medicines may make claims or indications that relate to weight loss in overweight, but not in obese, individuals. The links between obesity and cardiovascular health, sleep apnoea and osteoarthritis are well established. The serious[6] health risks associated with obesity require intervention and management by an appropriately qualified healthcare practitioner.

Medicines with indications that refer to obesity must be Registered. Registered medicines are individually assessed for quality, safety and efficacy prior to their inclusion on the ARTG and supply in Australia. Details of the requirements for Registered Medicines are included in the ARGCM Part I[7].

Several Registered medicines, including prescription medicines, are available for managing weight loss. Prescription medicines for weight loss are indicated for obese patients with a BMI > 30 kg/m^2 or BMI > 27 kg/m^2 if associated with co-morbidities. They are intended for use under the supervision of a doctor who can monitor their use and the health of the patient.

Mechanism of Action of Weight Loss Products

Medicines that support weight loss work by decreasing energy intake or increasing energy expenditure, or both. Medicines that aim to reduce energy intake (kilojoules/calories) may act on the brain or in the gastrointestinal tract to provide early satiation, to increase satiety or decrease the absorption of macronutrients such as fat or starch. Medicines that target energy expenditure may cause an increase in physical activity or metabolic rate.

[4]National Health and Medical Research Council 2003. Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults.
[5] World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity. WHO Technical report series 894, Geneva: WHO 2000
[6] Obesity meets the definition of serious in Part II of Schedule 6 of the Therapeutic Goods Advertising Code <link>. Medicines that make claims that they are for the treatment of serious conditions are generally not Listable
[7] Australian Regulatory Guidelines for Complementary Medicines (http://www.tga.gov.au/cm/cm.htm#argcm)

Although understanding the mechanism of action is useful supporting information that may be used in conjunction with primary evidence to strengthen or give emphasis to the wording of a claim, the measure of the success of a weight loss medication is its ability to bring about a decrease in BMI, weight or total body fat.

Levels of Evidence - Weight Loss & Listed Medicines

Claims and indications for weight loss for Listed medicines imply there is a relationship between using the product and a reduction in the weight of an overweight individual (BMI 25 to 29.9 kg/ m^2). A change in BMI, body weight or body fat content can be used to indicate weight loss, and to determine efficacy of the therapy.

A sponsor must be able to provide medium level evidence (as described in **Table 2 –** *Appendix 1*) to support products claims in relation to weight loss. General level evidence is not acceptable for demonstrating weight loss.

Medium level evidence is evidence from:

- well designed controlled trials without randomisation,
- well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies or from multiple time series with or without intervention.

High level evidence can also be used to support medium level claims and is preferred. High level evidence to support weight loss can be obtained from a systematic review of all relevant Random Control Trials (RCTs), or from at least one high quality, preferably multi-centre, RCT (see **Table 3 –** *Appendix 1*). If a systematic review is used to support a claim, it is important that the studies included in the review satisfy the requirements outlined for weight loss studies.

Traditional medicines may be used to support claims for certain Listed medicines. However, given the recent emergence of overweight and obesity as global health issues, claims for weight loss products are unlikely to be substantiated by well documented periods of traditional use.

Evidence of Successful Weight Loss

The success of a weight loss medication is determined by its ability to bring about a decrease in BMI, weight or total body fat of at least 5 percent of initial value AND at least 3 percent greater reduction in body weight or fat than placebo and/or controlled diet and physical activity.

Evidence of changes in body composition or body shape, while supportive, are not sufficient to demonstrate weight loss. Evidence of changes in body composition to support weight loss must be separately justified using validated measures for determining loss of body fat[8]. A claim that lean body mass increased and fat mass decreased without any weight loss indicates a change in body composition rather than in weight, and this would not be considered to meet the requirements for weight loss unless the decrease in the amount of body fat was quantified using a validated measure. Similarly, a change in waist circumference without a change in weight would not be sufficient to support a claim or indication for weight loss.

[8] All methods of measuring body fat are indirect and therefore subject to some uncertainty. Validated measures for body fat and lean tissue include, for example, dual energy X-ray absorptiometry (DEXA) and air displacement (BOD POD®). Techniques such as body impedance analysis (BIA) and skin fold thickness are not well validated for estimating body fat.

Clinically significant weight loss is defined as a reduction in the initial weight of an overweight individual by 5 percent or more. For individuals of average height, this is about 4–5 kg for males and 3–4 kg for females.

Claims that refer to appetite suppression, increased metabolic rate, increased satiety, thermogenic effect or other claims that otherwise could indirectly or by implication mislead a consumer to believe that the product was intended to assist in weight loss, should not be made unless the products meets the requirements for demonstrating effective weight loss or the claim explicitly states that the product is not indicated for weight loss.

Weight Loss Studies

Study Design

Scientific evidence for weight loss may be derived from case control studies, cohort studies or clinical trials. However, case control studies and cohort studies may not be practical means of establishing weight loss and are limited in their ability to produce unbiased and unambiguous data regarding the effect of a weight loss intervention. Clinical trials, particularly randomised and blinded trials provide the most robust information regarding the potential effects of an intervention.

Study characteristics

Subject Eligibility: Weight Category – BMI

Only human studies are considered sufficient to support indications and claims for weight loss for Listed medicines and participants must reflect the characteristics and lifestyle of the target population for the product. Suitable subjects should have a recognised problem with excessive weight but otherwise be healthy. Studies with subjects with a BMI of between 25 and 34.9 kg/m^2 for Caucasians (includes overweight and obesity class I – see **Table 1**) are considered relevant for predicting weight loss in a target population with a BMI of 25 to 29.9 kg/m^2. A different BMI range may be acceptable for subjects of non-Caucasian origin. For example, a BMI of between 23 and 33 kg/m^2 is more appropriate for those of Asian or South Asian ethnicity[9].

Subjects should also fit the following eligibility criteria, unless specifically directed to a specific population sub-group:

- Male and female subjects
- BMI between 25 and 34.9 kg/m^2 (for Caucasians)
- Generally healthy
- Age 18–60 years
- Should not include a specific phenotype such as type-2 diabetes.

Basal or resting metabolic rate (BMR) accounts for about 65-75 percent of daily energy expenditure. BMR is determined by a number of factors of which body size, gender, age and body fat are all important. Obese subjects have a higher BMR in absolute terms than lean individuals but a lower BMR when expressed per kilogram of body weight. These effects are greater depending on the BMI. In addition, obese persons expend more energy for a given activity because of their larger mass. Therefore, for the same level of dietary energy and physical activity, the magnitude of the effect will be different for obese and overweight subjects. As a result, weight changes observed in obese subjects with a BMI > 35 kg/m^2 are not applicable to overweight subjects.

[9] Allison, D. B. Fontaine, K. R. et al. (2001). Alternative treatments for weight loss: a critical review." Crit Rev Food Sci Nutr 41(1): 1-28; discussion 39-40.

In addition, studies that include severely obese subjects, subjects with co-morbidities such as type-2 diabetes or obstructive sleep apnoea or include specific population subgroups such as menopausal women should not be generalised to otherwise healthy overweight groups.

Number of Subjects

Sustained weight loss using weight loss products has generally been shown to be modest and there is usually great individual variation in response to therapy. It is important that trials enrol sufficient numbers of participants to detect a significant and reliable intervention effect. The number of subjects needed to be reasonably certain of a reliable result needs to account for the modest weight loss likely to occur, the variability of individual results and the number of subjects dropping out of the study.

Studies using only small numbers of subjects are only likely to detect very large differences in weight between those receiving the Listed medicine and controls. Further, the risk of small studies producing an unreliable result is very high. To reliably detect a weight loss of 5 percent, the minimum number of participants in the trial needs to be estimated prior to the start of the study.

In addition, the difference between those taking the Listed medicine and the control subjects would need to be at least 3 percent of body weight loss. Power calculations indicate that 34 controls and 34 subjects would be a minimum requirement to reliably complete the study to detect a 3 percent or greater weight loss in the intervention group. In determining the number of subjects, calculations were based on a weight change standard deviation of 5 percent, a *p*-value of 0.05 and statistical power of 0.8 and a one sided hypothesis. With dropout rates of 20-30 percent often experienced, at least 90 people would need to be recruited – 45 subjects and 45 controls would generally be needed.

As indicated above, high rates of attrition can introduce serious bias into a study and suggest caution in assessing the effectiveness of an intervention based on the weight loss of those who completed the program.

It is important to recognize that some trials of products citing positive effects for weight loss have been studies of small numbers of subjects

Sufficient evidence?

Example 1: 16 patients (BMI 25 to 32 kg/m^2) were randomised in two groups – one took a medicine called "Satisfied" and the other a placebo. After two months on their respective therapies, those who took "Satisfied" lost an average of 5.2 percent of initial body weight and those who took the placebo lost 2.5 percent. It appears that those taking "Satisfied" lost more weight, but while the average difference between the two groups was a loss of approximately 3 percent of body weight, the 95 percent confidence interval for the difference ranged from a weight gain of 1.4 percent to a weight loss of 7.4 percent for those taking "Satisfied". Therefore the difference was not statistically significant and the positive result may have been a chance finding. The study required more subjects to properly assess the effectiveness of this product. The current study does not support "Satisfied" for weight loss.

Example 2: A sponsor is using the results of a randomised, placebo controlled, double blind clinical study that shows that over a 24 hour period, subjects who took the product had a small but significant increase in metabolic rate over subjects taking a placebo, in support of a weight loss claim. However, the study did not examine the effect of the product on the actual weight of the subjects, and there is no other evidence showing that a short term increase in metabolic rate translates into any significant longer term weight loss. The claim for weight loss is not substantiated by this data. This is one of the most common deficiencies observed in substantiating indications and claims for medicines for weight loss. In particular, the study does not demonstrate that subjects have lost weight or indicate the relevance of the evidence to weight loss. For example, the increase in metabolic rate could concomitantly lead to increased appetite and energy intake.

observed for short periods. Studies with larger numbers of subjects over a longer period of time will provide more convincing evidence of effectiveness.

Intervention and control groups

All participants enrolled in a clinical trial are considered to be derived from a common population and may be allocated to control or intervention groups. Randomisation of participants to intervention and control arms of the trial helps eliminate innate intergroup differences and potential bias. Baseline characteristics of the intervention and control groups should always be documented to establish equivalence in key areas such as age, weight, diet and other factors that may contribute to non-intervention differences in weight loss between groups.

Interventions

Trials should be conducted under conditions where the only difference between groups is that one is exposed to the intervention whilst the other is not. Crossover studies, where the subjects and controls swap over and change roles, may be useful to demonstrate that weight loss is seen when taking the test product.

In most RCTs for weight loss, controlled diet and physical activity are included in all treatment arms, including the placebo group. Studies may demonstrate a significant weight loss, although it should be recognised that this can partly be attributed to diet and/or physical activity. The placebo-subtracted weight loss may be much more modest than the total weight loss observed in the clinical trial. In all trials the dietary advice, physical activity and behavioural programs must be of similar nature and intensity for both control and intervention groups.

Intensive management of diet, including energy and food choice, as well as physical activity in all arms of the study may limit the extent to which study results can be extrapolated to the consumer group targeted by the intervention– generally, this is the open-living, overweight, Australian population. The control of diet and physical activity in this environment, even with the intervention of a healthcare practitioner, is much more variable. A more realistic approach to better reflect community conditions would be to be less prescriptive about diet and physical activity.

Duration of Study

Numerous weight loss studies, whether testing medicine, diet or behavioural approaches, show most weight loss occurs early and that over time weight is usually regained towards baseline or even higher. For this reason, the duration of the trial is an important factor.

A reasonable maximum timeline to achieve a weight loss of 5-10 percent of initial body weight is six months. After about six months, the rate of weight loss usually declines as weight plateaus, and some regain is common. For these reasons, trials of less than six months are acceptable, with a minimum trial period of two months acceptable for demonstrating significant and sustainable weight loss. However, longer studies are preferable as there may be insufficient time in two months to demonstrate the full benefit, including the ability of the intervention to sustain weight loss for a longer period. Weight loss is never linear and to extrapolate the effects of early weight loss is misleading and not acceptable. Studies conducted over a few days or weeks provide unreliable results.

Outcome measures

To be considered effective, a Listed medicine must demonstrate a loss of at least 5 percent of initial bodyweight AND at least 3 percent greater reduction in body weight than placebo within two (and preferably within six) months of beginning therapy. Studies in which self-reported weights by subjects were the only indicators used to measure weight loss are not sufficient. Proxy measures, such as appetite suppression, changes in metabolic rate or body composition are also not sufficient For more information please refer to the **Evidence for Successful Weight Loss** heading earlier in this document.

Attrition Rates

Many studies of weight loss show high rates of subject attrition. This can introduce serious bias into these studies because the reasons for non-completion may be differential across initially randomised groups, diminish generalisability of the intervention and suggest caution in the interpretation of data based on the weight loss of those who remained in the program.

Assessing evidence from weight loss studies

Evidence submitted to support indications or claims for weight loss is assessed in terms of:

- *Level of evidence*: the types of study submitted must be consistent with those approved for medium level claims. Case control studies, cohort studies and clinical trials are appropriate to support claims for weight loss
- *Quality of evidence:* studies are critically appraised in terms of methodological quality and the possibility of bias and/or confounding. Studies that have been peer reviewed are more likely to be methodologically robust
- *Effect size and significance of evidence:* the results of studies are assessed for statistical and clinical significance. Studies used to support claims for weight loss must demonstrate a loss of at least 5 percent of initial bodyweight and at least 3 percent greater reduction in body weight than placebo
- *Relevance of evidence:* the findings of studies submitted must be relevant to the population targeted by the product, i.e. overweight individuals within the open Australian population.
- *Totality of evidence:* the balance and range of evidence available must support claims made by a weight loss product. The evidence used to substantiate a claim should agree with the surrounding body of evidence. If conflicts or inconsistencies exist, sponsors should seek plausible explanations to account for these.

For more information on levels of evidence please refer to **Table 3** in *Appendix 1*.

Studies of Listed Medicines with Multiple Ingredients

For multi-ingredient Listed products, indications and claims for weight loss can be based on the evidence for the product itself, or on evidence for an individual ingredient or a component in an ingredient. Where claims of synergy are made, the evidence must support the synergistic effect. When evidence supporting effective weight loss is based on a particular combination of ingredients, then the evidence only applies to that particular combination (ingredients, preparation, formulation, and posology) and cannot be extrapolated to any individual ingredients or similar combination on the basis on the positive results of the combination.

Labelling Requirements for Listed medicines Indicated for Weight Loss

The general labelling requirements for medicines regulated in Australia by the TGA are specified in Therapeutic Goods Order No. 69 (TGO 69) General requirements for labels for medicines and in the document Required Advisory Statements for Medicine Labels[10].
The information on the label of Listed medicines indicated for weight loss must be true, valid, not misleading and consistent with the evidence. The label must state:

A. Where based on scientific evidence:
   1. that the medicine may aid* (or assist or help) in weight loss
   2. the medicine should be used in conjunction with a (calorie- or kilojoule-) controlled diet and physical activity (or exercise) and
   3. to help (or assist) with weight loss, consult a healthcare practitioner.

B. Where based on evidence of traditional use for weight loss:
   1. that this (state traditional paradigm) medicine has been used traditionally** to aid (or assist or help) in weight loss and
   2. the medicine should be used in conjunction with a (calorie- or kilojoule-) controlled diet and physical activity (or exercise) and
   3. to help or assist with weight loss, consult a healthcare practitioner.

Notes:
* Indications that a medicine can prevent, treat or manage overweight are only appropriate for Registered medicines.
** Where scientific evidence is available to support an indication for weight loss for a traditional medicine, reference to its traditional use for this purpose need not be stated on the label.

[10] *General requirements for labels for medicines* and in the document *Required Advisory Statements for Medicine Labels* (http://www.tga.gov.au/meds/rasml.htm).

Appendix 1

The Regulation of Complementary Medicines

In Australia, medicinal products containing herbs, vitamins, minerals, and nutritional supplements, homoeopathic medicines and certain aromatherapy products are referred to as 'complementary medicines'. Australia has a two-tiered regulatory system for medicines, based on risk. Complementary medicines available for supply in Australia can be *Listed* or *Registered*. Listed medicines may only contain ingredients permitted by the TGA for use in low risk medicines. Listed medicines are restricted to indications and claims relating to health maintenance, health enhancement or non-serious, self-limiting conditions. Generally, they may not refer to a serious form of a disease, disorder or condition or indicate they are for treatment or prevention. More information about the regulation of complementary medicines in Australia is provided in the document *The Regulation of Complementary Medicines in Australia – an Overview*[11].

Listed medicines – Indications and Claims

In principle, indications considered appropriate for Listed medicines are those that can be safely and effectively used without the intervention of a healthcare practitioner. This includes diseases, disorders or conditions that are generally of a benign or self-limiting nature that the average consumer can be expected to evaluate or diagnose accurately. When determining if an indication is appropriate for a Listed medicine, it is important to consider whether delayed contact with a healthcare practitioner due to attempted self-medication, could lead to increased risk to the consumer.

The *Therapeutic Goods Act 1989* (the Act) requires that, at the time of Listing a medicine in the ARTG, a sponsor must hold the information or evidence to support indications and claims made in relation to the product. All indications and claims must be capable of substantiation – that is, evidence held by the sponsor must adequately demonstrate all indications and claims made for the product are true, valid and not misleading. Listed medicines are not subject to pre-market evaluation for efficacy at the time of Listing. For multi-component Listed products, evidence for the indications and claims can be based on the evidence for the product itself, or on evidence for an individual ingredient or component in an ingredient.

There are two types of evidence which may be used to support claims[12]. These are:

- scientific evidence and
- evidence based on traditional use of an ingredient or product.

Indications and claims[13] have been classified in three levels – general, medium and high (see **Table 2**). Different standards of evidence are required depending on the level of indication or claim made for a particular product. Consistent with low risk and the ability of a consumer to self-manage, Listed medicines may only carry general and medium level indications and claims and may not make reference to a serious form of any disease, disorder or condition[14]. The types of indications and claims permitted for Listed medicines include health maintenance, health enhancement and for

[11] The Regulation of Complementary Medicines in Australia: an Overview - http://www.tga.gov.au/cm/cmreg-aust.htm
[12] Evidence held to support indications and claims must be in the English language, or be a certified transcript translated from the native language
[13] Indication, in relation to therapeutic goods, means the specific therapeutic purpose of the product. Indications are for the purpose of market entry to record the therapeutic use of the product on the ARTG. Claims, in contrast, represent advertising statements about the product and need to be seen in the broader advertising context. The link between indications and claims is through Section 22(5) of the Act, which requires that sponsors may make only claims that are consistent with the indications for the product recorded on the ARTG.
[14] In the interest of public health some Listed medicines have been approved to refer to serious disease – sunscreens (skin cancer) and some nutrient supplements (calcium and osteoporosis; folic acid and neural tube defects).

symptomatic relief and risk reduction (other than for serious forms) of a disease, disorder, or condition (see **Table 2**).

Table 2 – Indications and claims permitted for Listed (low-risk) medicines.

Level of claim	Type of Indication or Claim
General	• Health maintenance, including nutritional support • Vitamin or mineral supplementation and • Relief of symptoms (not related to a named disease, disorder or condition).
Medium	• Health enhancement • Reduction of risk of a non-serious disease, disorder or condition • Reduction in frequency of a discrete non-serious event • Aids/assists in the management of a named symptom or non-serious disease, disorder or condition and • Relief of symptoms of a named non-serious disease, disorder or condition.
High	• Treatment, cure, prevention or management of any disease/disorder/condition • Reduction of risk or frequency of any serious disease, disorder or condition and • Relief of symptoms of any named serious disease, disorder or condition.

Where there is a public health or safety concern about the claim(s) for a product or range of products, or the claim(s) appear to be wilfully misleading, or in response to a complaint about the product, the TGA may call upon sponsors to provide the evidence they hold to support the claim(s) for review.

If the claims are not substantiated by the evidence, the product may be cancelled from the ARTG. To facilitate compliance with the requirement to hold evidence to support particular claims, Guidelines have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listed medicines (the Guidelines). Evidence to support claims can be based on scientific evidence, or evidence of traditional use.

Table 3 – Levels and Types of Scientific Evidence.

Level	Type of Evidence
High	Evidence obtained from a systematic review of all relevant randomised controlled trials, without significant variations in the directions or degrees of results. **OR** Evidence obtained from at least one properly designed randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice.
Medium	Evidence obtained from well designed controlled trials without randomisation. **OR** Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies. **OR** Evidence obtained from multiple time series with or without intervention, including within country and between country population studies. NOTE: In practice the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence. The evidence base of these sources must be high or medium level studies.
General	Descriptive studies, case series or reports of relevant expert committees. Texts, such as TGA-approved Pharmacopoeias or monographs, or other evidence based reference texts, are included in this Level.

Appendix 2

Glossary

Blinding
Blinding (also called masking) is a procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignment(s). Blinding is used so that neither the patients' nor staff's expectations about the medicine or treatment under investigation can influence the outcome.

Case study
In depth description of the factors related to a disease, disorder or condition in a specific individual.

Case-control study
A study that starts with identification of people with the disease, disorder or condition of interest (the cases) and a suitable control group without the disease or outcome (the controls). The relationship of an attribute (medicine, treatment, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and in the controls. For example, to determine whether thalidomide caused birth defects, a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Claim
A claim, in contrast to an indication, which is a description of the specific therapeutic purpose of a product, is an advertising statement about a product and needs to be seen in the broader advertising context. The link between indication and claim is through Section 22(5) of the *Therapeutic Goods Act 1989*, which requires that sponsors may make only claims that are consistent with the indications for the product recorded on the Australian Register of Therapeutic Goods.

Clinical significance
The assessment of clinical significance is usually based on the size of the effect observed, the quality of the study that yielded the data, and the probability that the effect is a true one. Clinical significance is not the same as statistical significance; a finding in a study may demonstrate a statistical difference in an attribute under review but this may have no impact clinically.

Clinical trial/clinical study (synonym: intervention study)
A planned study in humans designed to discover or verify:
- the clinical, pharmacological and/or other pharmacodynamic effects of a medicine or treatment and/or
- to identify any adverse reactions to a medicine or treatment and/or
- to study absorption, distribution, metabolism and excretion of a medicine or treatment, with the object of ascertaining its safety and/or efficacy.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)
An observational study in which a defined group of people (the cohort) are followed over time. The outcomes in subsets of the cohort are compared, for example to examine people who were exposed or not exposed, or exposed at different levels, to a particular intervention or other factor of interest. A cohort can be assembled in the present and followed into the future (this would be a prospective study or a "concurrent cohort study"), or the cohort could be identified from past records and followed from the time of those records to the present (this would be a retrospective study or a "historical cohort study"). Because random allocation is not used, matching or statistical adjustment

at the analysis stage must be used to minimise the influence of factors other than the intervention or factor of interest.

Condition
A simplified description for a disorder, which is a derangement or abnormality of function.

Control
In clinical trials comparing two or more interventions, a control is a person in the comparison group that does not receive the medicine or treatment under evaluation. Instead that person receives a *placebo*, no intervention, usual care or another form of care. In case-control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, to control means to adjust for or take into account extraneous influences or observations.

Controlled clinical trial
Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. Whilst not all controlled studies are randomised, all randomised trials are controlled.

Crossover trial
This is a research design in which subjects receive a number of treatments in sequence. Generally, this means that all subjects have an equal chance during the trial of experiencing both treatment and placebo dosages without direct knowledge, instead of either placebo or the treatment. Subjects may be transferred directly from one treatment to another or may have a washout period in between test treatments. This type of trial can be randomised so that all subjects don't get the alternative treatments in the same order.

Disease
Any deviation or interruption of the normal structure or function of any part, organ or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose aetiology, pathology and prognosis may be known or unknown.

Disorder
A derangement or abnormality of function.

Double blind
Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given during the course of the trial.

Efficacy
A relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Indication
Indication, in relation to therapeutic goods, means the specific therapeutic purpose of the product. Indications are for the purpose of market entry to record the therapeutic use of the product on the Australian Register of Therapeutic Goods (ARTG). Claims, in contrast, represent advertising statements about the product and need to be seen in the broader advertising context. The link between indications and claims is through Section 22(5) of the *Therapeutic Goods Act 1989*, which

requires that sponsors may make only claims that are consistent with the indications for the product recorded on the ARTG.

***p*-value**
The probability (ranging from zero to one) that the results observed in a study (or results more extreme) could have occurred by chance. In a meta-analysis the *p*-value for the overall effect assesses the overall statistical significance of the difference between the intervention groups, whilst the *p*-value for the heterogeneity statistic assesses the statistical significance of differences between the effects observed in each study.

Placebo
An inactive substance or treatment that supposedly has no treatment value. It is given to participants in clinical trials as a control against which to compare the effects of the test substance. In practice, placebos may also have positive or negative effects on trial participants.

Population studies
Investigations of a disease or condition using subjects from a defined population. A population is a closely distributed grouping from a single community that is characterised by both genetic and cultural continuity through several generations.

Protocol
All clinical trials are based on a protocol, which describes in advance who may participate in a trial, the length of a trial and the schedule of tests, procedures, medications and dosages.

Randomisation
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomised controlled trial (RCT)
An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

Statistical power
The probability that the null hypothesis will be rejected if it is indeed false. In studies of the effectiveness of healthcare interventions, power is a measure of the certainty of avoiding a false negative conclusion that an intervention is not effective when in truth it is effective. The power of a study is determined by how large it is (the number of participants), the number of events (e.g. strokes) or the degree of variation in a continuous outcome (such as weight), how small an effect one believes is important (i.e. the smallest difference in outcomes between the intervention and the control groups that is considered to be important), and how certain one wants to be of avoiding a false positive conclusion (i.e. the cut-off that is used for statistical significance)

Statistical significance
The probability that an event or difference is real or occurred by chance alone. It does not indicate whether the difference is small or large, important or trivial. The level of statistical significance depends on the number of patients studied or observations made, as well as the magnitude of difference observed. Statistical significance observed in a clinical trial does not necessarily imply clinical significance.

Subject/trial subject
An individual who participates in a clinical trial, either as a recipient of the medicine or treatment, or as a control.

Symptom
Any subjective evidence of disease or of a patient's condition, that is, such evidence as perceived by the patient.

Systematic review
An analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. Cochrane Reviews are examples of such systematic reviews. In a systematic analysis only those trials which meet a number of pre-set conditions in relation to research design (e.g. sample size, randomisation) are included in the final meta-analysis.

Washout period
The stage in a cross-over trial where treatment is withdrawn before a second treatment is given. This is usually necessary to counteract the possibility that the first substance can continue to affect the subject for some time after it is withdrawn.

A Quick Guide to Levels and Kinds of Evidence for Listed Medicines with Indications and Claims for Weight Loss*

- Listed medicines may be useful together with diet and physical activity for managing overweight
- Overweight is classified as a Body Mass Index (BMI) of 25 to 29.9 kg/m^2
- An overall weight loss of at least 5 percent of initial body weight or fat AND at least 3 percent greater reduction in body weight or fat than placebo must be demonstrated
- The minimum level of evidence to support weight loss claims is medium; high level evidence is more persuasive
- Evidence should be from studies that reflect the characteristics and lifestyle of the target population
- Studies with subjects with a BMI of between 25 and 34.9 kg/m^2 may be used for predicting weight loss in a population with a BMI of 25 to 29.9 kg/m^2
- Studies should include sufficient subjects to reliably estimate the effect is attributable to the product
- Studies should be a minimum of two months. A reasonable maximum timeline to achieve a weight loss of 5-10 percent of initial body weight is six months.
- Claims that refer to appetite suppression, increased metabolic rate, increased satiety, thermogenic effect or other claims that otherwise could indirectly or by implication mislead a consumer to believe that the product was intended to assist in weight loss, should not be made unless the products meets the requirements for demonstrating effective weight loss or the claim explicitly states that the product is not indicated for weight loss.
- Listed medicines may make claims or indications that relate to weight loss in overweight, but not in obese, individuals. The serious health risks associated with obesity require intervention and management by an appropriately qualified healthcare practitioner
- Product labels must refer to the importance of an energy-controlled diet, physical activity and the need to consult a healthcare practitioner

* This Quick Guide must be used in conjunction with the *Guideline for Levels and Kinds of Evidence for Listed Medicines with Indications and Claims for Weight Loss*