Medicines Adverse Reactions Committee

Meeting date	**8 March 2018**	Agenda item	3.2.1
Title	**Levonorgestrel emergency contraception and weight-based efficacy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Medicines	**Sponsors**	**Registration status**	
Postinor-1	CARSL Consulting	Consent given	
Postinor-2	Rex Medical	Approval lapsed	
Levonelle	Rex Medical	Approval lapsed	
Levonelle-1	CARSL consulting	Not available	
Next Choice	Teva Pharma	Not available	
Postrelle	Mylan	Not available	
Funding	1.5 mg tablets funded for a maximum of 2 tablets per prescription. May be provided by a pharmacist under the non-prescribing practitioners provisions in Part III of Section A of the pharmaceutical schedule.		
Previous MARC meetings	This was previously discussed at the 12 June 2014 meeting.		
International action	Reviewed by various regulatory agencies in 2014.		
Prescriber Update	None		
Classification	Mostly a prescription medicine but can be sold by nurses competent in the field of sexual and reproductive health and by pharmacists.		
Advice sought	**The Committee is asked to advise:** – On the strength of the evidence for a double dose to 3 mg of LNG-EC in heavier women. – On the strength of the recent evidence for the effects of BMI or weight on the efficacy of LNG-EC. – Whether updates to data sheets are necessary. – If this topic requires further communication other than MARC's Remarks in *Prescriber Update.*		

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1.0 PURPOSE

Levonorgestrel emergency contraception (LNG-EC) and weight-based efficacy was last reviewed by the Committee in June 2014. Since then, new information has become available from published studies. Medsafe has also become aware of New Zealand clinical guidelines that recommend doubling the dose of levonorgestrel to 3 mg when used in women over 70 kg or body mass index >26 kg/m^2 – this is an unapproved/off-label dose.

The purpose of this paper is to review recent information that has become available since the last review in 2014.

2.0 BACKGROUND

2.1 Levonorgestrel emergency contraception (LNG-EC)

Levonorgestrel is taken as a 1.5 mg tablet as soon as possible, preferably within 12 hours but no later than 72 hours, after unprotected sex [1].

The precise mode of action is not known. At the recommended dose, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if intercourse has taken place in the pre-ovulatory phase, when the likelihood of fertilisation is highest [1]. Levonorgestrel is not effective once the process of implantation has begun [1].

Efficacy appears to decline with increasing time between unprotected sex and starting treatment (95% within 24 hours, 85% within 24–48 hours, 58% if started between 48 and 72 hours) [1].

The alternative emergency contraception method available is the copper intrauterine device (IUD) which can be inserted up to 120 hours (or 5 days) after unprotected sex or the earliest expected date of ovulation.

2.1.1 Pharmacokinetic properties [1]

Absorption

Orally administered levonorgestrel is rapidly and almost completely absorbed.

Distribution

The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of single dose of 1.5 mg levonorgestrel maximum drug serum levels of 18.5 ng/mL were found at 2 hours.

After reaching maximum serum levels, the concentration of levonorgestrel decreased with a mean elimination half-life of about 26 hours.

Biotransformation

Levonorgestrel is not excreted in unchanged form but as metabolites.

Elimination

Levonorgestrel metabolites are excreted in about equal proportions with urine and faeces. The biotransformation follows the known pathways of steroid metabolism – the levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucuronide conjugates.

No pharmacologically active metabolites are known.

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only about 1.5% of the total serum levels are present as free steroid, but 65% are specifically bound to SHBG.

The absolute bioavailability of levonorgestrel was determined to be almost 100% of the dose administered.

2.1.2 Effects of weight

The World Health Organization defines obesity as BMI >30 kg/m^2 and overweight as BMI ≥25 kg/m^2.

Obesity is generally a complicating factor in physiology and in the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and hormones [2]. The increase in body weight, besides adding to the mass of excess adipose tissues, produces variable changes in renal, hepatic, endocrine and other organ functions [2]. In particular, there are higher serum oestrogen concentrations, lower progesterone concentrations, decreased luteinising hormone concentrations and altered rhythmic patterns of some of these during the menstrual cycle in obese women [3]. Often there are issues with normalising PK parameters for ideal or total body weight and whether to base doses on either ideal or total body weight or some intermediate factor [2].

Obesity has been proven to adversely affect the PK of combined oral contraceptives containing levonorgestrel and ethinylestradiol, in particular half-life and clearance. These in turn cause a delay in achieving maximum concentration (C_{max}) levels and steady state [4-8].

Levonorgestrel clearance is highly dependent on the availability of unbound drug [9]. Levonorgestrel is a highly bound drug, mainly to SHBG with only a small fraction unbound (2–3%) [10, 11]. In theory, drug clearance is a function of blood flow, drug enzyme/transporter activity (ie, intrinsic clearance) and plasma protein binding. For a low clearance drug like levonorgestrel, blood flow is less critical thus plasma protein binding and intrinsic clearance are highly influential. Compared to normal BMI women, levels of SHBG are lower in the obese [12]. Since levonorgestrel is bound to SHBG, free fraction of hormone could be elevated resulting in unpredictable effects on clearance [13]. It is also unclear whether SHBG associated increase in free fraction would also alter free concentrations, the pharmacologically active form of the drug [13].

Comments:

There is a range of drug metabolism alterations in obesity so there is a biological plausibility for changes in hormonal contraception effectiveness in obese women. However, these PK changes are not linearly related to BMI or weight and it is not known what degree of obesity begins to affect PK or PD processes.

It is thought that obesity can affect the PK of LNG-EC because the PK are similar to that of levonorgestrel-based oral contraceptives. However, baseline differences between normal and obese BMI emergency contraception users have not be studied until recently.

2.2 Summary of MARC's 2014 review

The paper presented to the Committee at the June 2014 meeting is attached as Annex 1. Minutes from the meeting are available on the Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes158.htm#3.2.4) and are summarised below.

This safety concern originated from a meta-analysis by Glasier et al (2011) [14] of two randomised controlled trials sponsored by HRA Pharma comparing the efficacy of levonorgestrel with ulipristal acetate for emergency contraception. HRA Pharma is the manufacturer of an emergency contraceptive medicine containing levonorgestrel.

The Committee noted that the two randomised controlled trials were designed to compare the efficacy of levonorgestrel with ulipristal acetate and were not initially designed to examine the effect of body weight on the effectiveness of emergency contraception. Data for the weight threshold where efficacy is reduced is limited.

The PK and PD relationship between dose and effect is not well defined. Evidence for a decrease in efficacy in heavier women is sparse. However, the Committee considered that women should be warned about a possible lack of effect in body weights >70 kg. The Committee noted the lack of

information on effectiveness of higher doses of levonorgestrel in heavier women and the potential usefulness of approaching the sponsor to examine this possibility.

The Committee noted that irrespective of weight, levonorgestrel may not prevent pregnancy in every case. However, it has good user acceptability and a favourable adverse effect profile compared to the available alternatives.

The Committee recommended that data sheets and consumer medicine information (CMI) for emergency contraceptives containing levonorgestrel be updated to include information on weight-based efficacy.

Comments:

At the time of the June 2014 meeting, the Committee noted the lack of information on effectiveness of higher doses in heavier women.

Levonorgestrel data sheets were updated following the Committee's review. Please refer to section 2.4.1 for relevant information now included in the data sheet.

2.3 Clinical guidelines

2.3.1 Family Planning (New Zealand)

Family Planning's advice on LNG-EC is available on their website: www.familyplanning.org.nz/advice/contraception/emergency-contraceptive-pill.

Their advice states the ECP is not as effective for women who weigh more than 70 kg and for these women a copper IUD is recommended. If a woman decides to take the ECP, they should take a double dose – two ECPs together.

2.3.2 Pharmaceutical Society of New Zealand (PSNZ)

New practice guidelines for provision of LNG-EC were released in July 2017 (Annex 2 – www.psnz.org.nz/Folder?Action=View%20File&Folder_id=119&File=PSNZ%20ECP%20Guidelines%202017.pdf) with a reminder emailed to pharmacists in November 2017. These new guidelines included information on the issue of weight/BMI on the efficacy of levonorgestrel emergency contraception.

These guidelines state that pharmacokinetic studies show serum concentrations of levonorgestrel in women with BMI >30 kg/m^2 are approximately half that of women with BMI <25 kg/m^2. As evidence has developed, various weights and BMIs have been reported in studies as being problematic. PSNZ has adopted the weight and BMI recommendations of the UK Faculty of Sexual and Reproductive Health (FSRH) which also aligns with Family Planning NZ advice.

The guidelines recommend a copper IUD if there is a high risk of conception and if it is within 5 days of unprotected sex. If the copper IUD is not an option, doubling the dose of levonorgestrel to 3 mg appears to increase its blood levels back to that of slimmer/lighter women. Pharmacists may offer to supply a double-dose but PSNZ does not currently have evidence to show that this is effective for preventing conception. Doubling the dose of levonorgestrel to 3 mg has not been approved by the manufacturer or Medsafe. A copper IUD is strongly recommended if BMI >30 kg/m^2 due to the high risk of failure.

A table on BMI and levonorgestrel ECP failure rates from Glasier et al (2011) is included in the guidelines.

Table 1: BMI and levonorgestrel ECP failure rates

BMI	% Failure Rate	Confidence Interval
< 25	1.3	0.8 – 2.2
25-29.9	2.5	1.3-4.6
30 or more	5.8	3.5 – 9.5
	No ECP: 5.6	

2.3.3 New Zealand Formulary (NZF)

Section 7.3.5 contains information on LNG-EC (http://nzf.org.nz/nzf_4244). This states there is some evidence that women weighing more than 70 kg or with a BMI over 26 kg/m^2 experience higher failure rates after taking LNG-EC. These women should be informed of the risk of treatment failure at the time of consultation and a double dose (3 mg) of levonorgestrel should be considered (unapproved dose). In addition, because it is not proven that a double dose of levonorgestrel is more effective, a post-coital IUD inserted within five days is recommended and should be discussed if the woman is at a high risk of pregnancy. A post-coital IUD provides the best emergency contraception especially for those women with a higher BMI.

Comments:

All NZ guidance (Family Planning, Pharmaceutical Society, NZF) indicate that in heavier women the IUD is the best emergency contraception available however a double dose (3 mg) of levonorgestrel can be considered if oral treatment is preferred or if IUD insertion is not an option.

2.3.4 UK FSRH clinical guidance on emergency contraception

The UK Faculty of Sexual and Reproductive Health (FSRH) clinical guidance on emergency contraception is publicly available: www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-emergency-contraception-march-2017/.

The guideline development group (GDG) considers the evidence suggests LNG-EC could be less effective in women weighing >70 kg or with a BMI >26 kg/m^2. If a copper IUD is not indicated or not acceptable, the GDG recommends that such women can be offered ulipristal acetate emergency contraception (UPA-EC). If UPA-EC is not suitable, a double dose (3 mg) of LNG-EC can be used.

The effectiveness of 3 mg LNG-EC for these women is unknown. However, the GDG considers that use of 3 mg LNG-EC (which is well tolerated and is supported by PK data) is justified by its potential ability to prevent unintended pregnancy more effectively than the standard 1.5 mg dose in women weighing >70 kg or with a BMI >26 kg/m^2. For women weighing >85 kg or with a BMI >30 kg/m^2, it is not known whether UPA-EC or 3 mg LNG-EC is more effective.

Comments:

The PK data referred to in these guidelines is from the Edelman et al (2016) study – see section 3.1.1 of this report.

UPA-EC is not approved for use in NZ. Emergency contraception options in NZ are LNG-EC or copper IUD.

2.3.5 Australian guidelines

[redacted] major guidelines from the Royal Australian College of General Practitioners (RACGP) 2017 and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2016 state that LNG-EC efficacy may be reduced with higher BMI, but do not recommend and increased dose [15, 16]. These guidelines state that ulipristal or copper IUD is more effective in obese women.

[redacted]

2.3.6 US guidelines

The American College of Obstetrics and Gynecology (ACOG) published a Practice Bulletin in 2015 [17]. This bulletin notes that LNG-EC may be less effective in women who are overweight or obese but does not recommend withholding oral EC because no research to date has been adequately powered to evaluate a threshold weight at which it would be ineffective.

2.4 Data sheets and information for consumers

2.4.1 New Zealand

Postinor-1 is the only approved LNG-EC currently available in NZ. The following information on weight is included in the data sheet.

4.4 Special warnings and precautions for use

> *Limited and inconclusive data suggest that there may be reduced efficacy of levonorgestrel with increasing body weight or body mass index (BMI) (see section 'Pharmacodynamics'). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.*

5.1 Pharmacodynamic properties

> *There is limited and inconclusive data on the effect of high body weight/high body mass index (BMI) on the contraceptive efficacy. In three WHO studies no trend for a reduced efficacy with increasing body weight/BMI was observed (Table 1), whereas in the two other studies (Creinin et al., 2006 and Glasier et al., 2010) a reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 2). Both meta-analyses excluded intake later than 72 hours after unprotected intercourse (i.e. off-label use of levonorgestrel) and women who had further acts of unprotected intercourse.*

Table 1: Meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010)

BMI (kg/m^2)	Underweight 0-18.5	Normal 18.5-25	Overweight 25-30	Obese ≥30
N total	600	3952	1051	256
N pregnancies	11	39	6	3
Pregnancy rate	1.83%	0.99%	0.57%	1.17%
Confidence interval	0.92-3.26	0.70-1.35	0.21-1.24	0.24-3.39

Table 2: Meta-analysis on studies of Creinin et al., 2006 and Glasier et al., 2010

BMI (kg/m^2)	Underweight 0-18.5	Normal 18.5-25	Overweight 25-30	Obese ≥30
N total	64	933	339	212
N pregnancies	1	9	8	11
Pregnancy rate	1.56%	0.96%	2.36%	5.19%
Confidence interval	0.04-8.40	0.44-1.82	1.02-4.60	2.62-9.09

The consumer medicine information (CMI) for Postinor-1 includes the following:

> *There is some evidence that Postinor-1 may be less effective with increasing body weight or body mass index (BMI), but these data were limited and inconclusive. Therefore, Postinor-1 is still recommended for all women regardless of their weight or BMI.*

Comments:

Please refer to section 3.2.1 for the meta-analysis on three WHO studies (Gemzell-Danielsson et al, 2015). The meta-analysis by Glasier et al, 2011 on studies of Creinin et al, 2006 and Glasier et al, 2010 was reviewed at the June 2014 meeting.

2.4.2 UK

The Levonelle UK data sheet includes the following information on weight.

4.4 Special warnings and precautions for use

> *Limited and inconclusive data suggest that there may be reduced efficacy of Levonelle 1500 with increasing body weight or body mass index (BMI) (see section 5.1). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.*

5.1 Pharmacodynamic properties

> *There is limited and inconclusive data on the effect of high body weight/high BMI on the contraceptive efficacy. In three WHO studies no trend for a reduced efficacy with increasing body weight/BMI was observed (Table 1), whereas in the two other studies (Creinin et al., 2006 and Glasier et al., 2010) a reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 2). Both meta-analyses excluded intake later than 72 hours after unprotected intercourse (i.e. off-label use of levonorgestrel) and women who had further acts of unprotected intercourse.*

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N total	64	933	339	212
N pregnancies	1	9	8	11
Pregnancy rate	1.56%	0.96%	2.36%	5.19%
Confidence Interval	0.04 – 8.40	0.44 – 1.82	1.02 – 4.60	2.62 – 9.09

The consumer medicine information for Levonelle includes the following:

> *There is some evidence that Levonelle 1500 may be less effective with increasing body weight or body mass index (BMI), but these data were limited and inconclusive. Therefore, Levonelle 1500 is still recommended for all women regardless of their weight or BMI.*

2.4.3 Australia

There is no published data sheet available for LNG-EC products. [redacted]

Comments:

Information in the NZ data sheet is in-line with the UK and Australia. Consumer medicine information also includes information on inconclusive data for weight-based efficacy.

3.0 SCIENTIFIC INFORMATION

3.1 Pharmacokinetic studies

3.1.1 Edelman et al (2016) – Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing [13]

This study is provided as Annex 3. The objective of this study was to determine if differences exist in the pharmacokinetics (PK) of levonorgestrel emergency contraception (LNG-EC) in obese and normal body mass index (BMI) users and test whether doubling the dose of LNG-EC in obese women increases total and free (active) LNG serum concentrations.

This study was conducted at Oregon Health & Science University in Portland, Oregon from March 2015 to August 2015. Healthy, reproductive-age women (18–35 years old) with obese BMI (≥30 kg/m^2) and normal BMI (<25 kg/m^2) received 1.5 mg LNG orally (ECx1) and then in a subsequent menstrual cycle following at least a one-cycle washout, the obese group also received a double dose of 3 mg LNG (ECx2). Dosing occurred during the follicular phase. Total and free LNG PK parameters were obtained via serum samples through an indwelling catheter at 0, 0.5, 1, 1.5, 2 and 2.5 h. The primary outcome was the difference in total and free LNG concentration maximum (C_{max}) between ECx1 and ECx2 in the obese group.

A total of 10 women enrolled and completed the study (normal BMI=5, median 22.8 kg/m^2, range 20.8– 23.7; obese BMI=5, 39.5 kg/m^2, range 35.9– 46.7). There were no notable differences in the baseline demographic characteristics, ovarian hormones, albumin or LH levels between the two BMI groups or between the obese cohorts two treatment cycles.

The total LNG C_{max} for obese subjects following ECx1 (5.57 ± 2.48 ng/mL) was significantly lower than the level observed in normal BMI women (10.30 ± 2.47, p=0.027) (Table 2). Notably, ECx2 increased the C_{max} significantly (10.52 ± 2.76, p=0.002); approximating the level in normal BMI subjects receiving ECx1. Calculated $AUC_{0\text{-}2.5h}$ total showed a similar pattern.

Levels of free LNG were approximately 1% of the total levels (Table 2, Figure 1). Although there was no significant difference in the free C_{max} between obese and normal BMI women that received ECx1 (0.065 ng/mL vs 0.089, p=0.37), the absolute proportion of free drug was somewhat higher in the obese group (1.2% vs 0.8%). A higher free C_{max} (0.126 ng/mL) was also seen in the obese ECx2 group as compared to both the obese ECx1 (0.065 ng/mL, 0.013) and the normal ECx1 (0.089 ng/mL, p=0.081). Again, the findings with free AUC were comparable.

Table 2: Pharmacokinetic parameters of exposure in obese and normal BMI women

	Obese ECx1	Normal ECx1	Obese ECx2
Cmax, total (ng/mL)	5.57±2.48a	10.30±2.47 (p=.027[b])	10.52±2.76 (p=.002[c])
Cmax, free (ng/mL)	0.065±0.038	0.089±0.033 (p=.37)	0.126±0.025 (p=.013)
AUC0-2.5 h, total (h*ng/mL)	9.05±4.95	17.62±5.89 (p=.056)	16.90±5.07 (p=.044)
AUC0-2.5 h, free (h*ng/mL)	0.096±0.056	0.145±0.054 (p=.250)	0.196±0.044 (p=.021)

[a] data represents mean ± S.D. of n=5 women.
[b] compared to Obese ECx1 using 2-tailed student t-test.
[c] compared to Obese ECx1 using paired t-test.

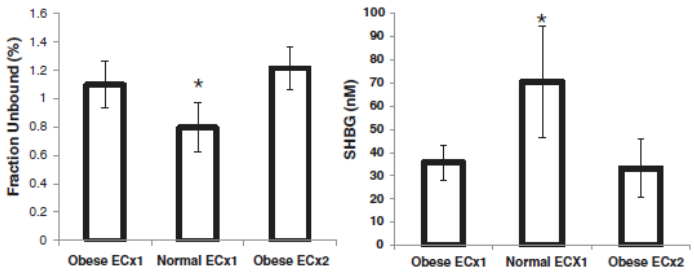

Figure 1: Fraction of LNG unbound (free-fraction) and SHBG levels
* denotes significantly (p<0.05) different from obese ECx 1. Each bar represents mean ± S.D. of n=5 women.

Concentration time curves are represented in Figure 2. The total concentration time curve for obese ECx2 mirrors the normal BMI ECx1 serum concentration time curve correcting the abnormality observed with ECx1 dosing. In terms of free concentration levels, the patterns are similar but the free LNG concentration level with ECx2 dosing exceeds the normal BMI ECx1 level. The higher fraction of LNG unbound in obese women likely explains this finding.

The fraction of LNG unbound or free fraction percentage was inverse to SHBG levels (Figure 1). Serum SHBG levels were significantly lower in obese compared to normal BMI women (70.4 nmol/L ± 21.6; p=0.015). SHBG levels were similar in obese BMI women between the two dosing regimens (ECx1 35.6 nmol/L ± 6.8; ECx2 33.2 nmol/L ± 11.2; p=0.42). Compared to normal BMI women, the increase in fraction unbound was approximately 35% in obese women at both doses (Figure 1).

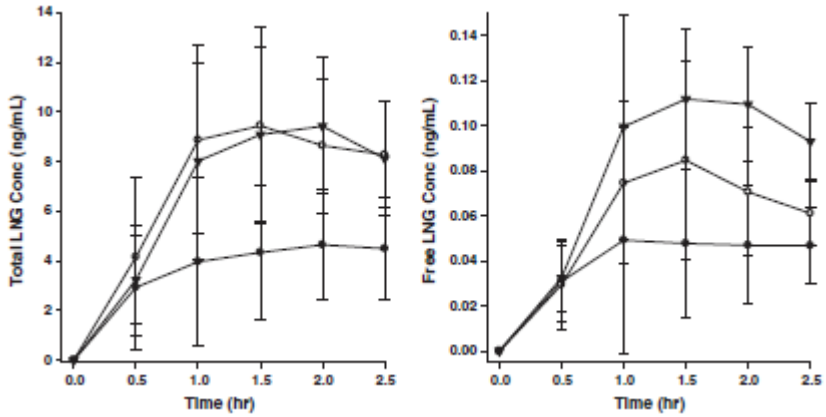

Figure 2: Concentration time curves for total (left panel) and free (right panel)
LNG serum concentrations (closed circle: obese ECx1, open circle: normal BMI ECx1, closed triangle: obese ECx2). Each data point represents mean ± S.D. of n=5 women

The authors conclude that obesity adversely impacts both the total and free C_{max} levels of LNG-EC and this likely explains its lack of efficacy in obese women. Doubling the dose appears to correct the obesity-related PK changes but additional research is needed to determine if this also improves EC effectiveness in obese women.

Comments:

There was no pharmacodynamic data obtained from this study. There was also no information on women with BMI 25–29 kg/m^2. Further AUC data is required as well as more research into whether doubling the dose to 3 mg improves effectiveness in obese women. However, the authors speculate that the direction of the changes correlates with the observed reduction in effectiveness seen in clinical trials.

3.1.2 Praditpan et al (2017) – Pharmacokinetics of levonorgestrel and ulipristal acetate emergency contraception in women with normal and obese body mass index [18]

This study is provided as Annex 4. The objective of this study was to compare the pharmacokinetics (PK) of levonorgestrel emergency contraceptive (LNG-EC) and ulipristal acetate (UPA-EC) between normal BMI and obese BMI women.

This prospective, randomised crossover study evaluated the PK of women after single doses of LNG-EC (1.5 mg) and UPA-EC (30 mg). Study procedures took place at Columbia University Irving Medical Center, New York, USA during clinical research unit admissions. Participants received a standardised meal and each study drug, in random order, during 2 separate 24 hour admissions from July to December 2015. Study staff collected 14 blood specimens (0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 h). The main outcome of this study was a comparison of between-group differences in AUC_{0-24}.

32 women completed the study (16 in each group) with a mean age of 30 (range 19–45) years. Using this sample size and the standard deviations (SDs) for $AUC_{0-\infty}$ listed in the LNG-EC and UPA-EC package inserts, a study of this size would be able to detect a difference of ≥50% in LNG $AUC_{0-\infty}$ and a difference of ≥32% in UPA $AUC_{0-\infty}$ between BMI groups with a power of 80% and a two-sided α of 0.05. Among normal BMI and obese BMI participants, the mean BMIs were 22.0 kg/m^2 (range 18.8–24.6) and 34.3 kg/m^2 (range 30.6–39.9), respectively.

Table 3 shows mean PK parameter estimates with interquartile ranges (IQRs) for measured total and calculated free LNG. Normal BMI and obese BMI women had differences in all LNG PK parameters. Figure 3 illustrates the difference between groups in AUC_{0-48} of total LNG.

Table 3: LNG-EC PK parameters in normal BMI and obese BMI women

	Total LNG		
Parameters[b]	Normal	Obese	p Value[c]
AUC (ng*h/mL)			
0-4 h	51.6 [23.7]	26.6 [16.5]	<.01
0–24 h	208.5 [74.2]	100.8 [35.8]	<.01
0–48 h	312.8 [134.6]	153.7 [46.0]	<.01
C_{max} (ng/mL)	18.2 [8.3]	10.8 [8.0]	<.01
T_{max} (h)[d]	2.0 [2.0]	3.0 [1.0]	.04
$t_{1/2}$ (h)[d]	27.0 [9.6]	50.4 [11.7]	<.01
V_d (mg/mL)[d]	186.9 [80.1]	709.9 [492.7]	<.01
Cl (L/h)[d]	4.8 [1.9]	9.8 [3.0]	<.01
	Calculated free LNG		
AUC (ng*h/mL)			
0-4 h	0.032 [0.012]	0.020 [0.011]	<.01
0–24 h	0.128 [0.025]	0.074 [0.021]	<.01
0–48 h	0.193 [0.056]	0.113 [0.027]	<.01
C_{max} (ng/mL)	0.011 [0.005]	0.008 [0.007]	<.01

[a] LNG, EC, PK, BMI.

[b] Parameters include AUC, maximum serum drug concentration (C_{max}), time to maximum serum drug concentration (T_{max}), elimination half-life ($t_{1/2}$), volume of distribution (V_d) and drug clearance (Cl). All parameters are reported as geometric means with [IQR], except T_{max}, which is reported as an arithmetic mean, with [IQR].

[c] Two-sided *t* tests.

[d] Mean values for total and calculated LNG [IQR] using method of Södergård et al. [8] and SHBG and albumin-binding affinities given by Nilsson and von Shoultz. [9]. The $t_{½}$ values shown here were calculated from the last 3 data points (16, 24 and 48 h); calculations based on 6 or 7 data points yielded comparable differences between groups.

After LNG-EC, mean AUC_{0-24} and maximum concentration (C_{max}) were 50% lower among obese BMI women than among normal BMI women (AUC_{0-24} 100.8 vs. 208.5 ng*h/mL, $IQR_{obese\ BMI}$ 35.8, $IQR_{normal\ BMI}$ 74.2, p≤0.01; C_{max} 10.8 vs. 18.2 ng/mL, p=0.01). The LNG T_{max} was later among obese BMI women and the $t_{1/2}$ was longer than among normal BMI women (T_{max} 3.0 h vs. 2.0 h, p<0.04; $t_{1/2}$ 50.4 h vs. 27.0 h, p<0.01).

After UPA-EC, AUC_{0-24} and C_{max} were similar between obese BMI and normal BMI women (AUC_{0-24} 362.5 vs. 293.5 ng*h/mL, $IQR_{obese\ BMI}$ 263.2, $IQR_{normal\ BMI}$ 112.5, p=0.15; C_{max} 95.6 vs. 89.3 ng/mL, p=0.70).

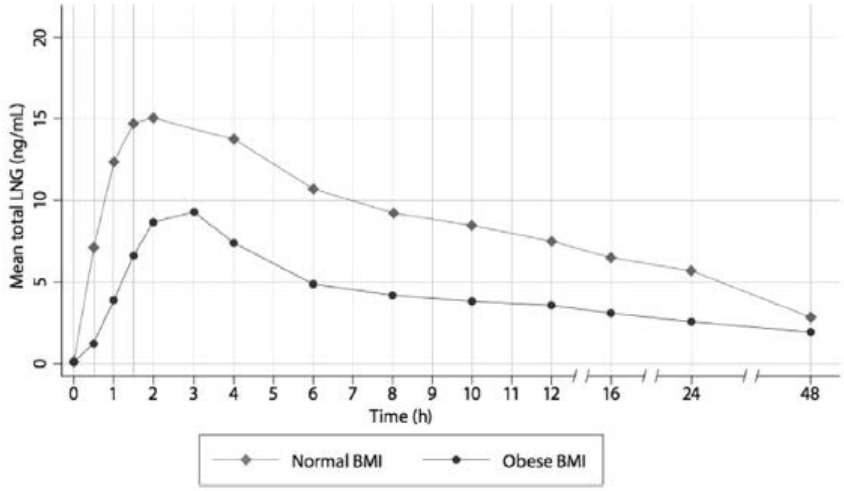

Figure 3: LNG concentration vs. time curve in normal BMI and obese BMI women

The authors conclude that after a single dose of EC, obese BMI women are exposed to lower concentrations of LNG and similar concentrations of UPA when compared to normal BMI women. The authors were unable to conclude that the PK differences observed explain the observed differences in LNG-EC and UPA-EC effectiveness by BMI; however, the lower LNG concentrations in obese women provide some support for the reported lower effectiveness.

Comments:

Findings from this study by Praditpan et al (2017) are similar to the findings of Edelman et al (2016). These findings have resulted in a hypothesis that obese women may require higher LNG-EC doses to achieve a therapeutic effect but a pharmacodynamic study is required to test this hypothesis.

3.2 Other studies

3.2.1 Gemzell-Danielsson et al (2015) – Impact of bodyweight/body mass index on the effectiveness of emergency contraception with levonorgestrel: a pooled-analysis of three randomised controlled trials [19]

The authors investigated whether higher bodyweight and/or BMI negatively impacted the risk of pregnancy in women receiving levonorgestrel emergency contraception (LNG-EC) after unprotected sex in a pooled analysis of 3 large multinational RCTs conducted by the World Health Organization (WHO).

The three RCTs conducted by the WHO Task Force on Postovulatory Methods for Fertility Regulation are briefly described here:

- Task Force on Postovulatory Methods of Fertility Regulation (1998) [20]: A comparison with the Yuzpe regimen (two doses of ethinylestradiol 100 mcg plus levonorgestrel 0.5 mg or *d,l* norgestrel 1.0 mg administered 12 hours apart) in which 1001 women (mean age 27.3 years) were allocated to receive LNG-EC administered as two doses of 0.75 mg taken 12 hours apart.
- von Hertzen et al (2002) [21]: A comparison with mifepristone (10 mg single dose) in which 1379 women were allocated to receive LNG-EC 1.5 mg as a single dose and a further 1377 women two doses of LNG 0.75 mg taken 12 hours apart. The mean age was 27 (range 14–52 years).
- Dada et al (2010) [22]: A comparison of single-dose LNG.EC 1.5 mg (n=1512) with LNG-EC administered as two doses of 0.75 mg taken 12 hours apart (n=1510) 5. The mean age was 26 years.

All analyses were done on the per-protocol set (PPS) which included 5812 women who received LNG-EC within 72 hours following unprotected sex. BMI and weight were represented in the same model. BMI was categorised with cut points at 18, 25, 30 and 35 kg/m^2 and bodyweight with cut points at 55, 65, 75 and 85 kg. The analysis was based on logistic regression with pregnancy as the outcome. A total of 56 pregnancies were available for analysis in the PPS.

Subject characteristics are described in Table 4. A subgroup of women (n=60) who were exceptionally short for their weight occurred almost exclusively in three of nine study groups in Nigeria. Notably, these subjects represented 1% of the sample but 4/59 pregnancies (6.8%). The findings were also in sharp contrast to the full African data where pregnancy risk was generally the lowest (0.5% including the contribution of these subjects) compared to other geographic regions.

Table 4: Characteristics of subjects and crude pregnancy rates

Characteristic	*N*	Mean (SD) or *n* (%)	Crude pregnancy risk (%) (95% CI)
Continuous variables			
Age	5862	27.0 (6.5)	N/A
Bodyweight (kg)	5859	59.5 (10.3)	N/A
Body height (cm)	5860	162.6 (6.7)	N/A
Body mass index (kg/m^2)	5859	22.5 (3.9)	N/A
Treatment delay (h)	5863	29.9 (18.7)	N/A
Expected probability of pregnancy (%)	5816	9.1 (10.9)	N/A
Length of menstrual cycle (d)	5863	28.8 (2.4)	N/A
Categorical variables			
Pregnant	5863		
No		5804 (99.0%)	N/A
Yes		59 (1.0%)	N/A
Body mass index (kg/m2) group	5859		
13.84–18.00		406 (6.9%)	1.7 (0.7 to 3.5)
18.03–25.00		4158 (71.0%)	1.0 (0.7 to 1.4)
25.01–29.93		1039 (17.7%)	0.6 (0.2 to 1.3)
30.02–34.89		202 (3.4%)	1.0 (0.1 to 3.5)
35.00–51.20		54 (0.9%)	1.9 (0.0 to 9.9)
Bodyweight (kg) group	5859		
30–54		2008 (34.3%)	1.3 (0.9 to 2.0)
55–64		2168 (37.0%)	1.1 (0.7 to 1.6)
65–74		1180 (20.1%)	0.6 (0.2 to 1.2)
75–84		399 (6.8%)	0.5 (0.1 to 1.8)
85–130		104 (1.8%)	0.0 (0.0 to 3.5)
Continent	5863		
Am/Aus/Eur		1255 (21.4%)	1.0 (0.5 to 1.7)
Africa		2683 (45.8%)	0.5 (0.3 to 0.9)
Asia		1925 (32.8%)	1.7 (1.2 to 2.4)
Treatment group	5863		
Single 1.50 mg		2461 (42.0%)	0.9 (0.6 to 1.4)
Double 0.75 mg		3402 (58.0%)	1.1 (0.8 to 1.5)
Further intercourse*#	5856		
No		3806 (65.0%)	0.9 (0.6 to 1.3)
Yes		2050 (35.0%)	1.2 (0.8 to 1.7)
Number of further acts of intercourse*#	2049		
1		699 (34.1%)	1.3 (0.6 to 2.4)
2		627 (30.6%)	1.1 (0.5 to 2.3)
>2		723 (35.3%)	1.0 (0.4 to 2.0)
Previous pregnancies	5863		
None		2110 (36.0%)	0.7 (0.4 to 1.2)
1 or more		3753 (64.0%)	1.2 (0.9 to 1.6)

Confidence intervals (CIs) for rate point estimates of 0.0% are one-sided 97.5% intervals.
N = number of non-missing observations.
*Current menstrual cycle.
#Protected intercourse. Women were advised not to have unprotected sex, and were given condoms. Participants were asked in the single studies to keep a diary of side-effects in the week after the treatment, and to record when a condom was used.

The observed unadjusted relationship between BMI, bodyweight and pregnancy is shown in Figure 4. There is an isolated hotspot around BMI 32.5 kg/m^2 and bodyweight between 55 and 74 kg. There is also a marginal ramp coinciding with a single pregnancy in subjects who are at the high end of the BMI and bodyweight range. Both these peaks are fully explained by the subgroup found within the three above-mentioned Nigerian study sites (they disappear from the heat map if these subjects are excluded). The probability plane being highly and irregularly curved indicated that a logistic

regression model would require higher order terms for a plausible fit. It is also evident that the effect of BMI is heterogeneous across levels of bodyweight and vice versa.

The estimated marginal effects associated with a unit increase in BMI from a defined reference level were mostly very close to neutral or had very wide CIs. One group of technically significant effects was located at reference BMI in the range 24 to 30 kg/m^2 and bodyweight between 50 and 65 kg with an odds ratio of up to 1.47 (95% CI 1.13–1.92). A single additional, very weakly significant effect (OR 2.18; 95% CI 1.03–4.62) appeared at BMI 44 kg/m^2 and bodyweight 80 kg.

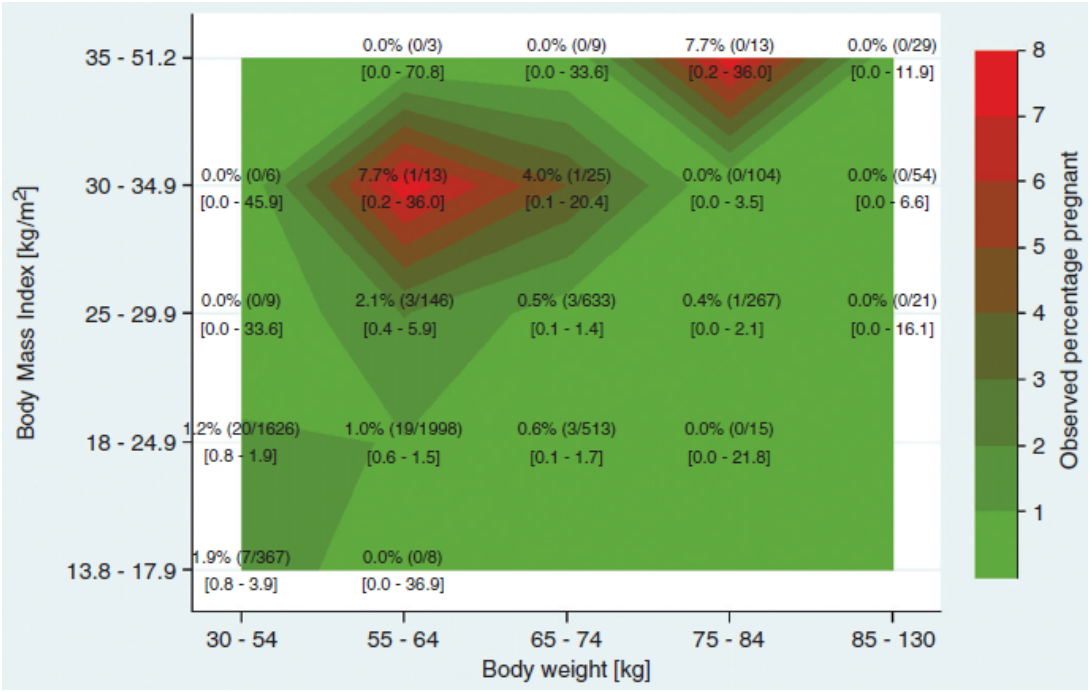

Figure 4: Empirical probability (%) heat map of pregnancy in subgroups defined by BMI and bodyweight
Figures in parentheses indicate numerators and denominators from which percentages were derived; those in square brackets indicate 95% CI for the percentages

The estimated effects of bodyweight were similar to those of BMI in terms of departure from neutrality and patterns of uncertainty. Statistically significant effects were located in the BMI range 26 to 30 kg/m^2 and bodyweight between 65 and 70 kg. At higher bodyweights relative to BMI, the risk of pregnancy decreased (Table 5).

Table 5: Odds ratios (95% CI) for pregnancy at selected levels of BMI and bodyweight relative to the odds at the reference point of 22.5 kg/m^2 and 60 kg

BMI\BW	40	45	50	55	60	65	70	75	80
18	2.15 (0.41–11.3)	1.51 (0.63–3.59)	1.83 (0.90–3.74)	2.62 (0.85–8.10)	2.98 (0.39–22.6)	N/A	N/A	N/A	N/A
20	N/A	1.80 (0.54–5.99)	1.32 (0.73–2.42)	1.26 (0.84–1.89)	1.19 (0.55–2.58)	0.86 (0.11–6.67)	N/A	N/A	N/A
22.5	N/A	N/A	2.16 (0.81–5.75)	1.42 (0.88–2.28)	reference point	0.67 (0.35–1.29)	0.38 (0.046–3.16)	N/A	N/A
25	N/A	N/A	5.17 (1.03–25.9)	3.10 (1.17–8.17)	1.74 (1.00–3.05)	0.94 (0.55–1.60)	0.50 (0.19–1.31)	N/A	N/A
30	N/A	N/A	N/A	13.7 (2.14–87.2)	10.9 (2.06–57.4)	4.53 (0.91–22.6)	1.32 (0.23–7.41)	0.35 (0.030–4.09)	N/A
40	N/A	N/A	N/A	N/A	N/A	N/A	12.5 (0.12–1339)	1.02 (0.0022–475)	0.011 (1.0×10^{-7}–1072)
50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	483 (1.69–138500)

* N/A indicates locations of insufficient sample coverage for effect estimation

The authors conclude that LNG-EC is effective for preventing pregnancy after unprotected intercourse or contraceptive failure and no evidence was found to support the hypothesis of a loss of EC efficacy in subjects with high BMI or bodyweight. Therefore, access to LNG-EC should not be limited only to women of lower bodyweight or BMI.

Comments:

This meta-analysis of three WHO studies is frequently quoted in data sheets for LNG-EC.

High BMI or bodyweight could not be confirmed as factors increasing the risk of pregnancy. The adjusted marginal effects of BMI that were significant can be explained by the subgroup of women who were exceptionally short for their weight.

A limitation of this study is that despite the large study population in the pooled analysis there were relatively small numbers of women in the high-BMI and high-bodyweight subgroups.

3.2.2 Kapp et al (2015) – Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception [23]

The authors evaluated the effect of body weight and BMI on the efficacy of LNG-EC.

Data from two large, multicentre, randomised controlled trials (RCTs) designed to assess EC efficacy were pooled to evaluate the effect of weight and BMI on pregnancy rates among women who received LNG. These two RCTs were used in the meta-analysis by Glasier et al (2011). The two studies had a similar design with 3 key exceptions: the time window for EC intake following unprotected sex, the LNG dosing regimen and reporting of weight and height:

- Creinin et al (2006) [24]: Women enrolled from 7 investigational sites in the US. Unprotected sex within 72 hours of seeking EC. Two doses of LNG 0.75 mg taken 12 hours apart. Weight and height measured.
- Glasier et al (2010) [25]: Included women from 35 investigational sites in the UK (10 sites), Ireland (1 site) and the US (24 sites). Unprotected sex within 120 hours of seeking EC. Single dose of 1.5 mg LNG. Weight and height self-reported.

Both studies were designed to demonstrate the noninferiority of ulipristal acetate (UPA) treatment compared with LNG among healthy women seeking EC after unprotected intercourse. Inclusion criteria for both studies were unrestricted in terms of body weight and BMI. The analyses were conducted on the primary efficacy evaluable populations as specified in each study protocol.

Several complementary analyses were performed to assess the effect of weight and BMI on pregnancy rates. The first statistical analysis compared the weight and BMI of women found to be pregnant versus those who were not pregnant following LNG treatment. The second analysis estimated the pregnancy rate in 5 prespecified classes of weight and BMI. These methods were not adjusted for major confounding factors but the relationship between the variables and the weight or BMI was estimated.

A logistic model including known confounding factors and the dichotomisation factor while maximising the R^2 of the model was retained to provide the best description of data assuming a stepwise relationship. Finally, cubic spline logistic regression modelling was performed to create a smoothing of the shape of the unadjusted relationship between weight/BMI and pregnancy rates.

The analysis population comprised 1731 women among whom 38 pregnancies were reported. Demographics and prognostic factors of EC failure in the study populations are shown in Table 6.

Table 6: Demographics and potential confounding factors of efficacy-evaluable population in the 2 studies analysed

	Study		
	Creinin, 2006 (*N*=773)	Glasier, 2010 (*N*=958)	Total (*N*=1731)
Weight (kg)			
Mean±SD (min, max)	65.9±14.7 (34.5, 136.0)	67.2±15.7 (39.5, 158.8)	66.6±15.3 (34.5, 158.8)
Categories, *n* (%)			
<55 kg	154 (20)	195 (20)	349 (20)
55–65 kg	288 (37)	320 (33)	608 (35)
65–75 kg	194 (25)	232 (24)	426 (25)
75–85 kg	61 (8)	94 (10)	155 (9)
≥85 kg	76 (10)	117 (12)	193 (11)
BMI (kg/m^2)			
Mean±SD (min, max)	24.1±5.2 (15.4, 54.7)*	25.1±5.6 (14.9, 53.7)*	24.7±5.5 (14.9, 54.7)
Categories, *n* (%)			
<20	118 (15)	131 (14)	249 (14)
20–25	421 (54)	452 (47)	873 (50)
25–30	147 (19)	220 (23)	367 (21)
30–35	52 (7)	97 (10)	149 (9)
≥35	35 (5)	58 (6)	93 (5)
Age (years), mean±SD	24.3±5.7	23.6±4.7	23.9±5.2
Race, *n* (%)			
Caucasian	566 (73)	692 (72)	1258 (73)
Black	110 (14)	175 (18)	285 (17)
Asian	52 (7)	19 (2)	71 (4)
Other	45 (6)	72 (8)	117 (7)
Conception probability (7)	5.37%	5.50%	5.44%
Further unprotected intercourse, *n* (%)	31 (4.0)	51 (5.3)	82 (4.7)
Time between unprotected intercourse and intake (h), mean±SD	35.3±21.6	39.7±25.7	37.6±24.1

* p=.001.

Women for whom LNG was not effective in preventing pregnancy had a significantly higher mean body weight and BMI than women who did not become pregnant (76.6 vs. 66.4 kg, p<0.0001; 28.1 vs. 24.6 kg/m^2, p<0.0001). The estimated pregnancy rate increased significantly from 1.4% (95%CI 0.5–3.0) among the group of women weight 65–75 kg to 6.4% (95%CI 3.1–11.5) and 5.7% (95%CI 2.9–10.0) in the 75–85 kg and >85 kg groups, respectively. Pregnancy rates by BMI category similarly demonstrated a highly significant trend across increasing BMI categories (Table 7).

Table 7: Pregnancy rate following LNG-EC according to BMI categories

	BMI (kg/m^2)				
	<20	20–25	25–30	30–35	≥35
N total	249	873	367	149	93
N pregnancies	4	11	9	10	4
Pregnancy rate	1.61%	1.26%	2.45%	6.71%	4.30%
95% CI[a]	0.44%–4.06%	0.63%–2.24%	1.12%–4.60%	3.26%–11.99%	1.18%–10.64%

[a] Exact Clopper Pearson method.

Statistical modelling demonstrated a steep increase in pregnancy risk starting from a weight near 70–75 kg to reach a risk of pregnancy of 6% or greater around 80 kg. Similar results were obtained for statistically modelling of BMI as well as when the two studies were analysed individually.

The authors conclude that all analyses showed a significant drop in the efficacy of LNG-EC with increasing body weight with a pregnancy risk in the higher weight categories similar to expected rates in the absence of contraception. Like body weight, increasing BMI was highly correlated with increased pregnancy risk.

Comments:

This study included the same 2 trials that were used in the meta-analysis by Glasier et al (2011) reviewed by the Committee in June 2014. Data from these trials were not designed to look at whether weight impacts the ability of EC treatment to prevent pregnancy. One of the trials (Glasier et al, 2010) included women who took EC within 120 hours of unprotected sex – LNG-EC is approved for use within 72 hours.

Despite the large data set, the number of pregnancies in the higher weight categories was small.

3.2.3 Festin et al (2017) – Effect of BMI and body weight on pregnancy rates with LNG as emergency contraception: Analysis of four WHO HRP studies [26]

The objective of this study was to estimate the effect of increased body weight and BMI on pregnancy rates with LNG-EC.

The study reviewed data from 6873 women in four WHO-HRP randomised trials on EC conducted between 1993 and 2010. Two of the trials were multicentre studies in collaborating sites from Africa, Asia, Australia, Europe and Latin America [20, 21]. The other two trials were single-country studies in Hong Kong [27] and Nigeria [22] (Table 8). Participants took either 1.5 mg of LNG as a single dose or in two doses 12 hours apart, up to 120 hours of unprotected intercourse. Contraceptive efficacy (pregnancy rates) at different weight and BMI categories was evaluated.

Table 8: Characteristics of WHO LNG-EC trials

Trial	EC regimen used in trial	Participating centres in countries	Number of LNG cases included in this analyses (sample size)
A. Hong Kong 1993 A prospective randomized comparison of LNG with Yuzpe regimen; Delay 0–48 h	Two LNG 0.75-mg doses with 12-h interval	1 centre in Hong Kong	410 (440)
B. WHO 1998 | RCT of LNG versus Yuzpe regimen; Delay 0–72 h	Two LNG 0.75-mg doses with 12-h interval	21 centres in 14 countries	974 (1001)
C. WHO 2002 | Low-dose mifepristone and two regimens of LNG; Delay 0–120 h	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	15 centres in 10 countries	2695 (2756)
D. Nigeria 2010 [A randomized double-blind study to compare two regimens of LNG; Delay 0–120 h	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	7 centres in Nigeria	2794 (3022)
Total pooled data	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	31 centres in 17 countries	6873 (7219)

Table 9 shows the main demographic characteristics of the women included. In the Hong Kong study, 6.6% of participants had BMI above 25 kg/m^2 compared to 36.8% in the Nigerian study.

Table 9: Demographic characteristics of participants from the included individual studies

Study and sample size	Hong Kong 1993 (*n*=410)	WHO 1998 (*n*=974)	WHO 2002 (*n*=2695)	Nigeria 2010 (*n*=2794)	Total pooled data (*n*=6873)
1. Mean age (SD)	26.6 (6.1)	27.3 (7.0)	27.2 (7.1)	26.6 (5.9)	27.0 (6.6)
2. Mean weight in kg (SD)	51.9 (6.6)	58.4 (10.4)	56.2 (8.7)	63.2 (10.5)	59.1 (10.3)
3. Weight categories, *n* (%)					
3a. Weight in kg < − 75	408 (99.8%)	901 (92.5%)	2609 (96.8%)	2384 (85.5%)	6302 (91.8%)
3b. Weight in kg 75–80	0	35 (3.6%)	35 (1.3%)	198 (7.1%)	268 (3.9%)
3c. Weight in kg 80 ++	1 (0.2%)	38 (3.9%)	51 (1.9%)	207 (7.4%)	297 (4.3%)
4. Mean height in cm (SD)	158.4 (6.7)	162.9 (6.4)	163.0 (6.1)	162.1 (7.5)	162.4 (6.9)
5. BMI categories as kg/m^2, *n* (%)					
5a. BMI (<− 25)	378 (93.3%)	821 (84.3%)	2469 (91.6%)	1760 (63.1%)	5428 (79.1%)
5b. BMI [25–30)	20 (4.9%)	127 (13.0%)	194 (7.2%)	799 (28.6%)	1140 (16.6%)
5c. BMI [30 ++)	7 (1.7%)	26 (2.7%)	32 (1.2%)	230 (8.2%)	295 (4.3%)

Table 10 shows pregnancy rates in various weight categories and BMI from the included studies. The overall pregnancy rate remains low in all studies at 1.2% (0.9–1.5). The rates remained low among women weighing over 80 kg (0.7%; 0.1%–2.7%) and who were obese (2.0%; 0.8%–4.6%).

Table 10: Pregnancy rates in various categories of weight and BMI from the included individual studies

Study and sample size	Hong Kong 1993 (410)	WHO 1998 (974)	WHO 2002 (2695)	Nigeria 2010 (2794)	Total pooled data (6873)
Number of pregnancies	12	10	44	17	83
Pregnancy rate	2.9 (1.3–4.6)	1.0 (0.4–1.7)	1.6 (1.2–2.1)	0.6 (0.3–0.9)	1.208 (0.95–1.47)
Pregnancies (N,%) by weight (kg) group					
a. Weight < − 75	11/408 (2.7%)	10/901 (1.1%)	44/2609 (1.7%)	14/2384 (0.6%)	79/6302 (1.3%)
b. Weight [75–80)	0	0/35 (0.0%)	0/35 (0.0%)	1/198 (0.5%)	1/268 (0.4%)
c. Weight [80 ++)	0/1 (0.0%)	0/38 (0.0%)	0/51 (0.0%)	2/207 (1.0%)	2/297 (0.7%)
Pregnancies (*N*, %) by BMI (kg/m^2) group					
a. BMI (<− 25)	10/378 (2.6%)	10/821 (1.2%)	42/2469 (1.7%)	6/1760 (0.3%)	68/5428 (1.3%)
b. BMI [25–30)	0/20 (0.0%)	0/127 (0.0%)	2/194 (1.0%)	5/799 (0.6%)	7/1140 (0.6%)
c. BMI [30 ++)	0/7 (0.0%)	0/26 (0.0%)	0/32 (0.0%)	6/230 (2.6%)	6/295 (2.0%)

Results from the adjusted regression model showing that BMI over 30 kg/m^2 or obesity provides a significant effect on efficacy (OR 8.27, 2.70–25.37) is shown in Table 11. This finding was mainly due to the pregnancies in women from the study site in Nigeria. Sensitivity analyses excluding the Nigerian site showed that obesity was no longer a risk factor; however, the other studies included too few obese women in the sample to exclude a substantial decrease in efficacy.

Table 11: Analyses of pregnancies and pregnancy rates from combined studies

Variable (all four studies)	Number of pregnancies	Number of women	Pregnancy Rate (%)	Odds ratio (95%C.I.)
BMI (< 25) kg/m^2	68	5428	1.25	1.00 (Ref)
[25–30) kg/m^2	7	1140	0.61	0.96 (0.42–2.21)
[30 ++) kg/m^2	6	295	2.03	8.27 (2.70–25.37)

The authors conclude pregnancy rates with use of LNG-EC 1.5 mg were low at less than 3% across different weight and BMI categories. Pooled analyses showed an increase in pregnancy rates among obese women (BMI more than 30 kg/m^2) compared to women with normal BMI levels, influenced by pregnancies all coming from one study site.

Comments:

This study includes women who took LNG-EC within 120 hours of unprotected intercourse but LNG-EC in NZ is approved for use within 72 hours.

Three of the four studies were included in the pooled analysis by Gemzell-Danielsson et al (2015) with an additional study conducted in Hong Kong. As with the results of Gemzell-Danielsson et al (2015), the Nigerian site influenced the increase in pregnancy rates seen among obese women.

3.3 Company reports

3.3.1 Gedeon Richter

[redacted]

[redacted]

3.3.2 Teva

[redacted]

3.4 CARM data

A search of CARM's database up to 31 December 2017 retrieved a total of 20 cases relating to LNG-EC. Of these 20 cases, 7 identify a lack of efficacy. Of these 7 cases, 3 reported the woman's weight and these are summarised in Table 12. Details of the 7 cases are attached as Annex 5.

Table 12: Reports to CARM describing lack of efficacy with LNG-EC with weight reported

Report	Date	Age	Reactions	Medicine(s)	Weight
099969	Feb 12	25	Medicine ineffective, Pregnancy unintended	Postinor-1	[redacted]
099970	Feb 12	38	Medicine ineffective, Pregnancy unintended	Postinor-1, citalopram, cetirizine	[redacted]
119418	Jan 16	37	Medicine ineffective, Pregnancy unintended	Postinor-1	[redacted]

3.5 Action taken by other regulators

[redacted]

3.5.1 [redacted]

[redacted]

3.5.2 [redacted]

[redacted]

[redacted]

Comments:

[redacted]

3.5.3 [redacted]

[redacted]

[redacted]

3.5.4 [redacted]

[redacted]

3.5.5 [redacted]

[redacted]

Comments:

[redacted]

3.5.6 European Medicines Agency (EMA)

A review was started in 2013 and concluded in July 2014 (www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002145.jsp&mid=WC0b01ac058004d5c1). The review was triggered when the data sheet for Norlevo was updated on the basis of results from two clinical studies to state that it is less effective in women weighing 75 kg or more and not effective in women weighing more than 80 kg.

The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended that emergency contraceptives containing levonorgestrel or ulipristal acetate can continue to be used in women of all weights as the benefits are considered to outweigh the risks.

Having assessed all the available evidence on the effectiveness of emergency contraceptives, the CHMP considered that the data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight. For LNG-EC, some clinical studies have suggested a reduced effectiveness in women with high bodyweight but in others no trend for a reduced effect with increasing bodyweight was observed. The CHMP recommended that the results of these studies should be included in the data sheets for emergency contraceptives and the current statement in the Norlevo data sheet should be deleted.

The CHMP considered that with generally mild side effects, the safety profile of emergency contraceptives is favourable and they can continue to be taken regardless of the woman's bodyweight.

Comments:

A more recent review on this topic could not be found. Current information in the Postinor-1 NZ data sheet is aligned with the Levonelle UK data sheet (see section 2.4.2).

4.0 DISCUSSION AND CONCLUSIONS

The Committee reviewed LNG-EC and weight-based efficacy in June 2014. This safety concern originated from a meta-analysis of two randomised controlled trials by Glasier et al (2011). Since then, further information from published studies have become available.

Two pharmacokinetic studies (Edelman et al, 2016 and Praditpan et al, 2017) investigated the effects of doubling the dose of LNG to 3 mg. Both studies showed that a double dose of LNG appears to correct obesity-related pharmacokinetic changes. However, there was no pharmacodynamic data from these studies and additional research is needed to determine whether these pharmacokinetic changes result in improved effectiveness in obese women.

Based on results from these two pharmacokinetic studies, clinical guidelines from the UK Faculty of Sexual & Reproductive Healthcare, Family Planning (New Zealand), Pharmaceutical Society of New Zealand and the New Zealand Formulary recommend that in heavier women the copper IUD is the best emergency contraception available however a double dose (3 mg) of levonorgestrel can be considered if oral treatment is preferred or if IUD insertion is not an option. Doubling the dose of LNG-EC to 3 mg is an unapproved/off-label dose. Clinical guidelines from the Royal Australian College of General Practitioners, Royal Australian and New Zealand College of Obstetricians and Gynaecologists and American College of Obstetrics and Gynecology do not recommend an increased dose of LNG-EC in heavier women.

Due to the limited data available, three studies (Gemzell-Danielsson et al, 2015; Kapp et al, 2015 and Festin et al, 2017) used pooled analyses of randomised controlled trials to increase the overall sample size and maximise the ability to detect any effect of body weight and/or BMI on pregnancy rates. However, despite the increase in sample sizes by using pooled data, the number of pregnancies in the higher weight/BMI categories are small resulting in imprecise estimates. In addition, analyses by Kapp et al (2015) and Festin et al (2017) included women who had taken LNG-EC within 120 hours of unprotected sex whereas the approved use of LNG-EC is within 72 hours.

Information on weight-based efficacy in the New Zealand data sheet and consumer medicine information for Postinor-1, the currently approved and available LNG-EC, is aligned with the UK data sheet and consumer medicine information for Levonelle. These were updated following the review in 2014 and currently state:

> *Limited and inconclusive data suggest that there may be reduced efficacy of levonorgestrel with increasing body weight or body mass index (BMI) (see section 'Pharmacodynamics'). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.*

5.0 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence for a double dose to 3 mg of LNG-EC in heavier women.
- On the strength of the recent evidence for effects of BMI or weight on the efficacy of LNG-EC.
- Whether updates to data sheets are necessary.
- If this topic requires further communication other than MARC's Remarks in *Prescriber Update.*

6.0 ANNEXES

1. June 2014 MARC paper
2. Pharmaceutical Society of New Zealand ECP practice guidelines
3. Edelman et al (2016)
4. Praditpan et al (2017)
5. CARM data

7.0 REFERENCES

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