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EMA/517526/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Referral under Article 13(2) of Regulation (EC) No 1234/2008

Levonelle 1500mcg tablets and associated names

INN: levonorgestrel

Procedure number: EMEA/H/A-13/1427

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 17 September 2014, Gedeon Richter Plc submitted an application for Levonelle and associated names through a mutual recognition procedure (MRP) type II variation (UK/H/0803/001/II/022) with the United Kingdom acting as a Reference Member State (RMS). The Concerned Member States (CMS) were: Austria, Belgium, Czech Republic, Germany, Greece, Spain, France, Ireland, Iceland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal and Sweden.

The applied variation was to add efavirenz to the list of medicines interacting with levonorgestrel (LNG) to the summary of product characteristics (SmPC) and package leaflet (PL) for Levonelle 1500 microgram (mcg) tablets.

The type II variation started on 17 September 2014. All Member States (MSs) supported the existence of a clinically relevant interaction however a few remained unsure about the advice on how to manage the interaction. Therefore the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh), under Article 13(1), paragraph 1 of Regulation EC No 1234/2008 by UK on 17 June 2015. The CMDh 60 day procedure was initiated on 3 August 2015. Day 60 of the CMDh procedure was on 1 October 2015, when a final position was reached by most MSs except Italy (IT). As no agreement could be reached, the procedure was referred to the CHMP.

On 1 October 2015, the United Kingdom (UK) as RMS triggered a referral under Article 13(2) of the Commission Regulation (EC) No 1234/2008. The CHMP was requested to give its opinion on whether a double dose of LNG 1500 mcg would be a suitable form of emergency contraception for patients taking concomitant hepatic enzyme inducers (mainly CYP3A4) after unprotected intercourse or failure of a contraceptive method, in particular women who are unwilling or unable to use non-hormonal methods, such as a copper-based intra-uterine device (Cu IUD).

The scope of this procedure is limited to Levonelle and associated names which are authorised in the European Union (EU) as emergency hormonal contraceptives (EHC). Levonelle 1500mcg and associated names consists of a single tablet.

2. Scientific discussion

2.1. Introduction

The referred MRP concerns a type II variation to add efavirenz (EFV) to the list of medicines interacting with LNG to the SmPC and PL for Levonelle 1500mcg.

Levonelle and associated names consists of a single tablet containing 1500mcg, or two tablets of 750mcg of LNG and it is approved for emergency contraception within 72 hours after unprotected intercourse or failure of a contraceptive method. The product is available over the counter (OTC) in 14 out of the 18 MSs involved in the procedure.

Currently, the SmPC and PL for this and other LNG emergency hormonal contraceptives (EHC) products, list a number of enzyme inducers which may affect contraceptive efficacy but do not provide advice on appropriate management of the interaction. The latter contrasts with the SmPC for other contraceptives containing LNG, which for both combined oral contraceptives and progestogen-only contraceptives containing LNG includes standard advice for users of enzyme inducers. For short term users the advice is to use additional barrier methods during and for 4 weeks after cessation of treatment until the time it takes for induced enzymes to subside. For long term users the advice is to use alternative methods.

The initial variation application at national level was prompted by a pharmacokinetic (PK) study by Carten et al. (2012), which showed marked reductions in plasma AUC, C_{max} and in $t_{1/2}$ of LNG following 14 days administration of efavirenz 600mg (the recommended daily dose for adults). This was a drug-drug interaction (DDI) study using LNG alone at levels used for EHC. Interactions with other CYP-inducing medicines have been extrapolated from studies involving combined oral contraceptives, which have lower LNG levels. The Carten et al. (2012) study thus prompted the questions of how this reduction in exposure to EHC should be managed and whether other enzyme inducers reduced LNG EHC plasma levels by a similar magnitude.

It should be noted that other LNG-containing EHC products are authorised in various MSs (either as alternative branded products and/or as generic formulations). Approved products are available either in packs of single 1500mcg tablets or as two 750mcg tablets, however all products are recommended to be taken as a single 1500mcg dose. Consequently, any recommendations applied to Levonelle also have relevance for other LNG EHC products.

2.2. Clinical efficacy

In order to support adding efavirenz to the product information as an interacting medicine, the application dossier was based on a study by Carten et al. (2012). In addition, the effect of efavirenz on LNG has been evaluated in two published studies so far (Scarsi et al., 2014 and Sevinsky et al., 2011).

Specific data for interactions of other enzyme-inducers with EHC doses of LNG are not available however the MAH presented studies following treatment with St John's Wort and combined hormonal contraceptives (CHC) administered with several enzyme inducers such as oxcarbazepine, carbamazepine, phenytoin, eslicarbazepine and perampanel.

There are limited data to support the lack of efficacy of LNG-containing contraceptives with concomitant use of CYP3A4 enzyme inducers, however the applicant presented a small pharmacodynamic study (Croxatto et al., 2004), two parallel group studies (He et al., 1990, 1991) and an additional study (Kesseru et al., 1973).

2.2.1. PK studies EFV-LNG

Carten et al. (2012) examined the effect of EFV on LNG EHC exposure with and without steady-state 600mg/day efavirenz (the recommended daily dose for adults) in 21 HIV-negative women receiving 2 tablets of 750mcg LNG 12h apart. As blood sampling was conducted until 12 hours post-dose, LNG exposure data correspond to the 750mcg LNG dose (half of the usual EHC dose) taken by this time point. Co-administration of efavirenz decreased LNG AUC_{0-12} by 58% (Geometric Mean Ratio (GMR) EFV to control (90% CI): 0.42 (0.36, 0.48)) and C_{max} by 45% (GMR EFV to control (90% CI): 0.55 (0.49, 0.63)). The coefficient of variation (CV)% of PK parameters were back-calculated, and are presented in the Table 1. This measure is a composite of both inter- and intra-subject variability.

Table 1: PK parameters of LNG with and without efavirenz (data from Carten et al., 2012)

	LNG alone GM	**CV%**	**LNG = EFV GM**	**CV%**	**n**
AUC_{0-12} (ng*hr/ml)	42.9	33.6	17.8	39.0	21
C_{max}	8.4	27.6	4.6	44.7	21

It is noted that the study design used the first licensed dosing regimen of Levonelle (2 tablets of 750mcg, 12 hours apart) rather than the currently licensed posology of a single 1500mcg dose.

The MAH highlighted that the study of Carten et al. (2012) is in accordance with the Guideline on the investigation of drug interactions[1] as both drugs were dosed at their clinically relevant doses and regimes (steady state for EFV and single (although split) dose for LNG).

Information on interactions with other CYP-inducing medicines has been extrapolated from studies involving combined oral contraceptives, which have lower LNG levels.

Scarsi et al. (2014) and Clayden (2015) examined the effect of antiretroviral therapy (ART) on exposure to LNG released from sub-dermal contraceptive implants (75 mg LNG/rod, two-rods) in HIV-positive Ugandan women. This non-randomised parallel group study included 3 arms: n=18 control group (no ART), n=20 stable nevirapine (NVP) therapy, n=20 stable EFV therapy. Efavirenz co-administration resulted in a 48% decrease of LNG $AUC_{0\text{-}36week}$ (GMR EFV to control (90%CI): 0.52 (0.51, 0.53)). By contrast, NVP co-administration resulted in a 32-39% increase in LNG concentrations (compared to the control group). The geometric means for LNG alone and LNG+EFV treatment, together with 90% CIs and back-calculated CV% of $AUC_{0\text{-}36week}$ (ng*week/ml) are presented in Table 2. The LNG concentration levels were 45-57% lower in the EFV group than in the control group throughout the 48 weeks of the study, despite lower average body weights in the EFV group.

Table 2: $AUC_{0\text{-}36week}$ of LNG with and without efavirenz (Clayden, 2015)

LNG GM	90%CI lower	90%CI upper	N	CV%	LNG+EFV GM	90%CI lower	90%CI upper	N	CV%
22.24	18.55	25.92	17	38.0	11.6	9.38	13.83	20	48.2

Sevinsky et al. (2011) studied the PK of an oral contraceptive containing ethinylestradiol and norgestimate after 2 CHC cycles, with and without co-administration of clinical dose of efavirenz (600 mg/day) in HIV-negative women. The pharmacokinetics of LNG (one of the active metabolites of norgestimate) was assessed in a post-hoc analysis from data in 6 patients. EFV coadministration resulted in an 80% reduction of C_{max} (GMR EFV to control (90%CI): 0.20 (0.17-0.23)) and 83% reduction of AUC (GMR EFV to control (90%CI): 0.17 (0.13, 0.21)). No calculation of CV% was possible for this reference.

It is known that CYP2B6 polymorphism causes higher EFV levels in slow metabolizers (Holzinger et al., 2012) and pronounced CYP3A induction (Habtewold et al., 2013). Despite this effect the variance in LNG PK parameters is not substantially increased in case of EFV co-administration, as shown in the tables 1 and 2.

- **Linearity of LNG PK in the dose range 750 – 3000mcg**

A study examining dose-proportionality of LNG in a wide dose range is not available, however conclusions about dose-proportionality of PK parameters can be drawn based on separate results in different dose ranges, as presented in Table 3. Another complicating factor is that in some studies LNG data are available only when co-administered with an oestrogen. According to these results the AUC is dose proportional in the 100-500 mcg dose range, however there are limited data to conclude about dose-proportionality in higher dose ranges.

[1] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

Table 3: Dose-proportionality of LNG AUC and C_{max}.

Reference	study drug	dose	PK parameter	comparison	GMR	90%CI Lower	90%CI Upper	IntraCV	conclusion
study code: 64932	Loette tablet containing 0.100 mg LNG and 0.020 mg EE	single dose (1,3,5 tablets), n=33	dose norm. AUC_{0-t}	0.3 mg/0.1 mg	0.90	0.84	0.96	11.9%	dose-proportional within the 100-500 µg dose-range
				0.5 mg/0.3 mg	0.96	0.91	1.02	10.9%	
				0.5 mg/0.1 mg	0.87	0.81	0.93	11.9%	
			dose norm. C_{max}	0.3 mg/0.1 mg	0.79	*0.70*	0.90	23.7%	less-than-proportional in the 100-300 µg dose-range
				0.5 mg/0.3 mg	0.94	0.84	1.06	21.4%	dose-proportional within the 300-500 µg dose-range
				0.5 mg/0.1 mg	0.75	*0.67*	0.84	20.9%	
study code: 02162	LNG 1.5 mg tablet and LNG 0.75 mg tablet	single dose 1.5 mg, 2*0.75 mg (12 h apart), n=15	$AUC_{0-\infty}$	1.5 mg/0.75 mg	0.85	0.81	0.90	7.9%	single dose bioequivalent with split doses 12h apart
			dose norm. C_{max}	1.5 mg/0.75 mg	0.67	*0.60*	*0.75*		less-than-proportional in the 0.75-1.5 mg range
study code: 2990	LNG 1.5 mg tablet, Plan B 0.75 mg tablet	single dose 1.5 mg, 2*0.75 mg (together), n=29	$AUC_{0-\infty}$	1.5 mg/2*0.75 mg	1.02	0.93	1.12	19.9%	the two formulations are bioequivalent
			C_{max}	1.5 mg/2*0.75 mg	1.02	0.92	1.12	22.7%	
Johansson et al 2002	LNG 0.75 mg tablet	single dose 1.5 mg (2*0.75 mg together), 2*0.75 mg (12 h apart), 2*0.75 mg (24 h apart), n=5	$AUC_{0-\infty}$	1.5 mg/2*0.75 mg (12h)	2.09	1.63	2.67		single dose NOT bioequivalent with split doses 12h apart
				1.5 mg/2*0.75 mg (24h)	2.14	1.49	3.08		single dose NOT bioequivalent with split doses 24h apart
			dose norm. C_{max}	1.5 mg/2*0.75 mg (12h)	0.78	*0.46*	*1.31*		less-than-proportional in the 0.75 -1.5 mg dose range
				1.5 mg/2*0.75 mg (24h)	0.73	*0.54*	1.00		

Re-analysis of Johansson et al (2002) data by the MAH on AUC_{0-12h} values provide indirect evidence about dose-proportionality of AUC in the 750-1500 mcg dose range: the GMR of AUC_{0-12h} is 0.86 (95%CI: 0.71, 1.11) and 0.89 (95%CI: 0.65, 1.13) for the 1.5 mg/2x0.75 mg (12h apart) and 1.5 mg/2x0.75 mg (24h apart) comparison respectively, showing that AUC is approximately dose-proportional in this dose range as well (taking into account the truncated nature of the estimate and the small sample size: n=5).

Most results show a less-than-proportional increase in C_{max} with dose increase (in the 100- 300 mcg and 750-1500 mcg dose ranges). LNG PK data with higher than 1500mcg doses are not available, either from the MAH's own data or from literature sources. Therefore no conclusion on linearity of PK parameters can be drawn in this dose range. The administration of higher than 1.5 mg LNG doses was discussed in an historic review of once-a-month contraceptive pills in China (Kejuan et al., 2007). One type of once-a-month pills contains 3 mg quinestrol and 6 mg LNG. LNG levels were reported to peak at 37.9±11.3 ng/ml and fall below limit of detection 9 days after the first pill intake. Surprisingly the authors reported a 5.6 times higher peak after the second pill intake with no further rise after the third pill. No other PK parameters of LNG were given. C_{max} values obtained after administration of 1.5 mg LNG were mainly between 18-20 ng/ml (Devoto et al., 2005 and Johansson et al., 2002). The 37.9 ng/ml C_{max} after 6 mg LNG shows less-then-proportional increase when compared to the 18-20 ng/ml C_{max} values obtained after administration of 1.5 mg LNG, however data are too scarce to draw any firm conclusion.

In vitro data provide indirect evidence on PK linearity in the clinically relevant dose range. LNG is a high bioavailability drug (87-100%; Hümpel et al., 1978, Goldzieher 1989), explained by its complete absorption and low hepatic extraction (Hümpel et al., 1978). The Michaelis-Menten parameters V_{max} and $K_{M,app}$ for LNG determined in vitro in human livers microsomes were 3.082 nmol/min/mg and 38.51 µM, respectively (Kuhnz and Gieschen, 1998). The maximal plasma concentrations of LNG in humans were 18-20 ng/mL (~ 58-64 nM) and 37.9 ng/mL (~ 121 nM) after doses of 1.5 mg and 6 mg, respectively (Devoto et al., 2005; Kejuan et al., 2007). Since LNG's peak plasma concentrations (C_{max})

are far lower than its $K_{M,app}$ value, non-linearity as a consequence of saturation of metabolism is highly unlikely in the pharmacologically relevant dose range.

Carten et al. (2012) has shown that co-administration of efavirenz decreased LNG EHC (2 x 0.75 mg LNG 12h apart) AUC_{0-12} by 58% and C_{max} by 45%. This level of decrease was confirmed by the study of Scarsi et al. (2014) (48% decrease in LNG $AUC_{0-36week}$) using the same EFV dose but different LNG dose (two-rod (75 mg/rod) LNG sub-dermal implant), as they were studying LNG sub-dermal contraceptive implants, not EHC. Therefore we can conclude that EFV used at its clinical dose causes an approximately 50% reduction of LNG exposure. The proposed dosage adjustment of 2x1.5 mg LNG for efavirenz co-administration can be fully justified given the 48-58% decrease in LNG exposure caused by efavirenz coadministration, provided that the approximate dose-proportionality of AUC values seen at a lower dose range holds for 3 mg as well, suggested by the available in vitro data as well.

In addition, a small PK study in obese women vs normal BMI women has been recently published (n=5) per group (Edelman et al., Contraception, 2016, in press). This study found that C_{max} and $AUC_{(0-2.5h)}$ of total LNG was doubled when a double dose of LNG EHC (3000mcg LNG) was used in obese women, suggesting that linearity of C_{max} is maintained to 3mg dose. Considering all the limitations of this study (sparse PK sampling for only 2.5h post-dose, lack of PD data, sample size), conclusions can be drawn only on C_{max} linearity. AUC has been calculated for a too short lifetime.

2.2.2. LNG with other enzyme inducers

The metabolism of LNG is significantly enhanced by concomitant use of CYP3A4 enzyme inducers. This is fully in line with the current SmPC of LNG and the literature review did not reveal any unexpected results. The evidence shows that some inducers, i.e. carbamazepine, efavirenz, eslicarbazepine, oxcarbamazepine, phenytoin, perampanel or St. John's wort are able to decrease AUC of LNG of more than 30% (see Table 4 and Table 5), i.e. showing a potentially clinically significant interaction.

Table 4: Effect of different CYP3A4 inducers in pharmacokinetic parameters of LNG

CYP 3A4 INDUCERS						Geometric mean ratio (90% CI) for X versus control			Reference
Object dose	Precipitant	Precipitant dose	In vivo induction	n	AUC % change	C_{max}	AUC	CLss/F	
30 µg EE/ 150 µg LNG	brivaracetam	400 mg/day for 20 days		23	-22	0.90 (0.85,0.95)	AUC_{τ} 0.78 (0.72, 0.83)	1.30	Stockis 2013
50 µg EE/ 250 µg LNG	carbamazepine	300 mg/day for 8-12 weeks	strong 3A4	1	-57		AUC_{0-24} 0.43		
50 µg EE/ 250 µg LNG	carbamazepine	400 mg/day for 8-12 weeks	strong 3A4	1	-30		AUC_{0-24} 0.70		Crawford 1990
50 µg EE/ 250 µg LNG	carbamazepine	600 mg/day for 8-12 weeks	strong 3A4	2	-35		AUC_{0-24} 0.65		
20 µg EE/ 100 µg LNG	carbamazepine	600 mg/day for 2 months	strong 3A4	10	-46	0.78	AUC_{τ} 0.54		Davis 2011
0.75 mg LNG subdermal LNG implant (2 rods,75 mg LNG/rod)	efavirenz	600 mg/day for 14 days	moderate 3A4	21	-58	0.55 (0.49, 0.63)	AUC_{0-12} 0.42 (0.36, 0.48)	3.31	Carten 2012
	efavirenz	600 mg/day, stable therapy	moderate 3A4	38	-48		$AUC_{0-36week}$ 0.52 (0.51, 0.53)		Clayden 2015
35 µg EE/ 250 µg NGM	efavirenz	600 mg/day for 14 days	moderate 3A5	6	-83	0.20 (0.17-0.23)	AUC_{τ} 0.17 (0.13, 0.21)		Sevinsky 2011
30 µg EE/ 150 µg LNG	eslicarbazepine	800 mg/day for 15 days		20	-17	1.04 (0.95, 1.14)	$AUC_{0-\infty}$ 0.83 (0.76, 0.91)	1.21	Falcão 2013
30 µg EE/ 150 µg LNG	eslicarbazepine	1200 mg/day for 15 days		20	-36	0.87 (0.79, 0.95)	$AUC_{0-\infty}$ 0.64 (0.56, 0.72)	1.63	
3 phasic OC, 30 µg EE/ 125 µg LNG on profile day	oxcarbazepine	900 mg/day for 25 days		10	-36	0.93*	AUC_{0-24} 0.64*		Klosterskov Jensen 1992
50 µg EE/ 250 µg LNG	oxcarbazepine	1200 mg/day for 26 days		16	-47	0.75	AUC_{τ} 0.53		Fattore 1999
50 µg EE/ 250 µg LNG	phenytoin	200 mg/day for 8-12 weeks	strong 3A4	3	-33		AUC_{0-24} 0.67		
50 µg EE/ 250 µg LNG	phenytoin	250 mg/day for 8-12 weeks	strong 3A4	1	-46		AUC_{0-24} 0.54		Crawford 1990
50 µg EE/ 250 µg LNG	phenytoin	300 mg/day for 8-12 weeks	strong 3A4	2	-46		AUC_{0-24} 0.54		
30 µg EE/ 150 µg LNG	perampanel	single 6-mg dose			no	C_{max} and AUC_{0-72} were not altered			
30 µg EE/ 150 µg LNG	perampanel	4 mg/day for 21 days			no	C_{max} and AUC_{0-24} were not altered			NDA 202834
30 µg EE/ 150 µg LNG	perampanel	8 mg/day for 21 days			-9	no signif. effect	AUC_{0-24} 0.91		
30 µg EE/ 150 µg LNG	perampanel	12 mg/day for 21 days			-40	0.58	AUC_{0-24} 0.60		

*: arithmetic mean ratio

For St. John's wort (SJW), one PK study with LNG EHC was identified. No lack of efficacy (LOE) cases were found in the literature when co-administrating LNG EHC with SJW, but 6 LOE cases were identified in the MAH's safety database (see section 2.2.3).

The effect of St. John's wort on the PK parameters of sensitive CYP3A4 substrates (midazolam and alprazolam) were studied and are summarised in Table 4 below. It is described in the literature that different SJW products have different CYP3A4 inducing capacity even at the same dose, mainly due to different hyperforin contents of the extracts (Mueller 2006). This table affirms the high variability of induction magnitude, nevertheless it also shows the potential for clinically significant interaction of CYP3A4 substrates (including LNG) and long-term administration of SJW.

Table 5: Effects of St. John's wort on pharmacokinetic parameters of sensitive CYP3A4 substrates

St. John's Wort							Geometric mean ratio (90% CI) for X versus control				
Dose of St. John's wort	Object	admin.	Dose	n	AUC%	CL%	C_{max}	AUC		CL/F	Reference
600 mg/day for 14 days	midazolam	Oral	7.5 mg	42	-22%		1.09 (0.63, 1.55)	AUC_{0-12}	0.78 (0.63, 0.95)		Mueller 2006
900 mg	midazolam	IV	0.05 mg/kg	12	-7%	9%		$AUC_{0-\infty}$	0.93	1.09	Wang 2001
900 mg	midazolam	Oral	5 mg	12	-21%	25%	0.67	$AUC_{0-\infty}$	0.79	1.25	
900 mg/day for 4 days	alprazolam	Oral	1 mg (3subj) 2 mg (4subj)	7	+70%		1.15*	$AUC_{0-\infty}$	1.70*		Markowitz 2000
900 mg/day for 10 days	midazolam	IV	2 mg	30		56%				1.56 (1.43, 1.69)#	Xie 2005
900 mg/day for 10 days	midazolam	Oral	5 mg	30		182%				2.82 (2.55, 3.25)#	
900 mg/day for 12 days	midazolam	Oral	4 mg (Oral) + 1mg (IV)	20		44%	0.51*			1.44	Dresser 2003
900 mg/day for 14 days	midazolam	IV	0.05 mg/kg	12	-21%	27%		$AUC_{0-\infty}$	0.79	1.27	Wang 2001
900 mg/day for 14 days	alprazolam	Oral	2 mg	12	-54%	127%	0.91*	$AUC_{0-\infty}$	0.46*	2.27	Markowitz 2003
900 mg/day for 14 days	midazolam	Oral	5 mg	12	-52%	109%	0.57	$AUC_{0-\infty}$	0.48	2.09	Wang 2001
900 mg/day for 14 days	midazolam	Oral	7.5 mg	42	-80%		0.35 (0.13, 0.57)	AUC_{0-12}	0.20 (0.09, 0.32)		Mueller 2006
900 mg/day for 56 days	midazolam	IV	0.05 mg/kg	12	-6%	3%		$AUC_{0-\infty}$	0.94	1.03	Hall 2003
900 mg/day for 56 days	midazolam	Oral	5 mg	12	-41%	53%	0.79	$AUC_{0-\infty}$	0.59	1.53	
1200 mg/day for 14 days	midazolam	Oral	7.5 mg	42	-32%		0.66 (0.39, 0.92)	AUC_{0-12}	0.68 (0.58, 0.78)		Mueller 2006
1800 mg/day for 14 days	midazolam	Oral	7.5 mg	42	-38%		0.70 (0.58, 0.82)	AUC_{0-12}	0.62 (0.47, 0.77)		
2700 mg/day for 14 days	midazolam	Oral	7.5 mg	42	-21%		1.01 (0.56, 1.46)	AUC_{0-12}	0.79 (0.70, 0.87)		
2700 mg/day for 14 days different SJW product	midazolam	Oral	7.5 mg	42	-48%		0.61 (0.30, 0.92)	AUC_{0-12}	0.52 (0.42, 0.62)		

*: arithmetic mean ratio #: 95% confidence interval

- Murphy et al. (2010)[2] conducted a small PK study (36 participants) with SJW. Participants received either 6 weeks of placebo or SJW 900 mg or 1500 mg daily; followed by either one 1.5 mg or 2.25 mg dose of the emergency hormonal contraceptive, LNG, taken between days 9-12 of a normal menstrual cycle. Serum progesterone levels were measured at weekly intervals. Pharmacokinetic modelling showed that LNG clearance increased with increasing amounts of SJW.

For carbamazepine one PK/PD study with combined oral contraceptives was identified as relevant:

- Davis et al. (2011) reported a double-blind, randomised, placebo-controlled cross-over study 10 healthy women given carbamazepine with a low-dose combined oral contraceptive (containing 20 mcg ethinylestradiol and 100 mcg LNG). The PK showed significantly lower AUC for LNG (53% of control) and ethinylestradiol in those women taking the carbamazepine and the contraceptive. Higher rates of ovulation and breakthrough bleeding were also seen with carbamazepine, although this was not statistically significant, likely because of the small sample size.

In addition one study and two case reports with LNG subdermal implants and anticonvulsants were identified as relevant:

- Haukkamaa (1986) investigated the effects of phenytoin on the level of LNG plasma concentrations and pregnancies with (Six) Norplant subdermal capsules (Silastic capsules, each filled with 36 mg

[2] Summary data from this study are available on the USA ClinicalTrials.gov website (see https://clinicaltrials.gov/ct2/show/study/NCT00131885?sect=X98701)

LNG) inserted into nine epileptic women, and ten control women using no medication. At 3 to 12 months, the overall mean concentration of plasma LNG was significantly lower in the six epileptic patients taking phenytoin alone or in combination with other anticonvulsants than in the controls. After one year, nine of the control patients continued the use of Norplant and no pregnancies occurred. Two of the nine epileptics became pregnant during contraception by Norplant. They both used phenytoin and their plasma concentrations of LNG were low near the time of conception.

- Odlind and Olsen (1986) reported the case of a 26-year-old woman, treated with phenytoin for 10 years because of epilepsy, who had Norplant subdermal implants (six Silastic capsules, each containing 36 mg of LNG) inserted after a legal abortion. She became pregnant again after nine months of Norplant use. Her plasma LNG levels were followed for one month during phenytoin treatment and then later during one month after discontinuation of phenytoin. During phenytoin treatment, plasma LNG levels were markedly below and plasma levels of sex hormone binding globulin (SHBG) were markedly above those found in normal healthy women and the woman had regular ovulatory menstrual cycles. After cessation of phenytoin, there was a pronounced, statistically significant increase in plasma LNG levels and SHBG decreased significantly. The woman's cycles became irregular and during the study period of one month, no signs of ovulation were found.
- Shane-McWhorter et al. (1998) reported the case of a 21-year-old woman with a history of a seizure disorder, treated with phenobarbital, who received LNG implants (Norplant, six Silastic capsules, each containing 36 mg of LNG) who became pregnant. After a normal delivery, she took oral contraceptives concomitantly with phenobarbital. Although she was educated about the importance of a backup method of contraception, the woman again became pregnant and delivered twins.

Finally one study with the LNG-releasing intrauterine system (LNG IUS; Mirena) was identified:

- Bounds and Guillebaud (2002) reported on the results of 56 women. Most took enzyme-inducers for epilepsy (medication taken by survey population included: carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, primidone, rifabutin, ritonavir, topiramate, many patients were on a combination of drugs). They have accumulated 1454 months of use of LNG IUS, of which 1075 months represent exposure to pregnancy risk. Only one apparently true LNG IUS failure has been documented, representing a failure rate of 1.1 per 100 woman-years (95% CI 0.03–6.25). The 42 year-old women who conceived was on primidone 500 mg and phenytoin 300 mg daily.

2.2.3. Relevance of the different dosing regimens

The LNG 1500 mcg tablet was authorised based on the results of a World Health Organization (WHO) study (von Hertzen et al., 2002, submitted as the Pivotal study) and an MAH sponsored PK study in healthy female volunteers (Anapharm Study Synopsis, unpublished). The latter demonstrated similar exposure from a single dose of one LNG 1500 mcg tablet compared to two doses of LNG 750 mcg tablets taken 12 hours apart, under fasting conditions ($AUC_{0-\infty}$ = 85.15% (80.90% to 89.61%)). The Pivotal study showed that a single dose of 1500 mcg LNG simplified the use of LNG for emergency contraception and showed better compliance of the patients compared to the administration of 750 mcg LNG tablets twice (12 hours apart) without loss of efficacy and without an increase in side-effects. Therefore, it is believed that the difference between the two products in their PK profile is not considered as clinically relevant. Moreover, such finding is supported by various other studies, where the two dose regimen showed comparable efficacy and safety and comparable PK data (e.g. Johansson et al., 2002).

- A small pharmacodynamic study found comparable efficacy of 750 and 1500mcg LNG using disruption of ovulation as an endpoint (Croxatto et al., 2004) (see extracted table 6 below).

Table 6: Proportion of cycles without follicular rupture or with ovulatory dysfunction within 5-day period following administration of the standard or single LNG dose or placebo

Classification	12–14 mm		15–17 mm		≥18 mm		Total	
	n	%	n	%	n	%	n	%
Standard dose								
No rupture	15/18	83	8/22	36	2/17	12	25/57	44
Ovulatory dysfunction	2/18	11	12/22	55**	6/17	35	20/57	35***
Single dose								
No rupture	17/18	94*	9/22	41	2/16	13	28/56	50
Ovulatory dysfunction	1/18	6	10/22	45*	9/16	56	20/56	36***
Placebo								
No rupture	10/18	56	8/22	36	2/16	13	20/56	36
Ovulatory dysfunction	1/18	6	2/22	9	0/16	0	3/56	5

Significantly different from placebo. Fisher's exact probability test.
* p=0.02, ** p=0.003, *** p<0.001

Croxatto et al. (2004) was a randomised double-blind cross-over study in which 58 women aged 18-40 with regular menstrual cycles in the preceding three months were monitored for ovulation from day 8 of the follicular phase. All women received placebo in one cycle and standard (2 x750mcg tablets 12 hours apart) or single (1 x750mcg tablet, i.e. half) dose in two other cycles, in a randomised order separated by resting cycles, so each woman contributed with three treatment cycles. Placebo or LNG was administered once the dominant follicle reached a pre-set size. The ovulatory process was monitored during the ensuing 5-day period (i.e. the time frame while spermatozoa may retain their fertilizing capacity in the female genital tract). Ovulation was defined by follicular rupture preceded 24–48 h by a normal gonadotropin surge and followed by a luteal phase, i.e., serum progesterone concentration over 12 nmol/L, in at least two samples taken during the luteal phase. Ovulatory dysfunction was defined by follicular rupture preceded by the absence or a blunted luteinizing hormone (LH) peak, or not followed by elevation of serum progesterone over 12 nmol/L.

- Two studies by He and co-workers (He et al., 1990; He et al., 1991) compared the pharmacokinetics and effectiveness of 750mcg Postinor (i.e. associated name to Levonelle) and a Chinese manufactured pill which also contained 750 mcg LNG but was not bioequivalent.

  Pharmacokinetics was studied in 10 healthy female volunteers in a cross-over study (He et al., 1990). Both sets of tablets were confirmed to contain 750mcg LNG (range for Chinese tablets = 90-105%; range for Postinor tablets = 96-101%). Absorption of LNG was lower and slower from the Chinese preparation than from Postinor, with significant differences in C_{max} and AUC_{0-24} between preparations (see extracted Table 7).

Table 7: PK data of the Chinese preparation and Postinor 750mcg

Mean ± SD	Chinese 750 microgram LNG	Postinor 750 microgram
C_{max} (ng/ml)	5.9 ± 1.7*	11.2 ± 3.4
T_{max} (h)	3.1 ± 1.2*	1.9 ± 0.6
AUC_{0-24} (ng/ml/h)	64.4 ± 21.9*	92.2 ± 34.3
$AUC_{0-\infty}$ (ng/ml/h)	92.3 ± 28.8	124.0 ± 42.8

*denotes statistically significant difference between Postinor and the Chinese pill

The pharmacokinetic differences were attributed to differences in particle size and dissolution rates, with the Chinese tablets having larger particle sizes and incomplete dissolution compared to LNG 750mcg tablets.

The dosing schedule in the trial differs from the posology of Levonelle, where the 1500 mcg tablet has to be taken once, and not later than 72 hours after unprotected intercourse. At the same time it is clear that Cmax of both experimental treatment regime (2x750 mcg LNG 24 hours apart) is lower than that of Levonelle tablet. Based on the pharmacokinetic study comparing the Hungarian Postinor and Chinese tablet the bioavailability of LNG from the Chinese tablet is lower than that of Postinor, which demonstrates similar phenomenon to that arisen by the interaction of efavirenz with LNG (Carten et al., 2012). Considering this and the comparative efficacy study of the Chinese tablet and Postinor it can be hypothesised that significantly lower doses of LNG may be similarly effective as the current Levonelle dose.

- Kesseru et al. (1973) studied the contraceptive efficacy of LNG doses ranging from 150 mcg to 400 mcg per tablet taken immediately and no later than 3 hours following intercourse.

  This clinical trial tested LNG doses ranging from 150 mcg to 400 mcg per tablet in 4631 women aged 15 to 48 years who had had at least one previous pregnancy. Treatment was started on the first day of the cycle to eliminate the possibility of an existing early pregnancy, and women were instructed to take one tablet after each sexual intercourse, preferably immediately and no later than 3 hours later. Calendar forms were used to collect information on intercourse, tablet intake and vaginal bleeding. Total exposure equalled 41802 months of use.

  Exposure to 400 mcg LNG represented the largest group, with 2801 patients studied, 71% for >6 months and 48% for >12 months, in all 25 558 months. There were 75 pregnancies in this group, yielding a failure rate of 3.52% and a corrected method failure rate of 1.69%. The incidence of pregnancies was higher in the groups treated with lower doses. Data from women taking 300, 350 or 400 mcg tablets who completed twelve months of use estimated that approximately 50% of women had intercourse 5 to 8 times per month and 22.5% of women had intercourse 9 to 12 times per month and 22.2% less than 5 per month during the first year of treatment.

  The time window for the treatment was much shorter compared to the current Levonelle SmPC, but also the dose used was reduced (maximum dose was 400 mcg vs. 1500 mcg). For women having frequent intercourse, the dose could be higher than the nominal dose (if more than one tablet was taken per day), although this dose (i.e. 2-3 x 400 mcg LNG per day) is still below the current treatment regimen of Levonelle.

The Croxatto et al. (2004) study measured ovulatory function when LNG was taken in the follicular phase, i.e. prior to ovulation. Disruption of ovulation may not be the only mechanism of LNG EHC action and other mechanisms of LNG EHC action were not studied. Moreover, during routine clinical use proximity to ovulation in relation to LNG EHC intake is not known. It is unclear how the reduction in efficacy with time since unprotected intercourse (see above) relates to timing in relation to ovulation.

The studies by He et al. (1990, 1991) and Kesseru et al. (1973) both involved taking LNG within a much narrower time frame than allowed by the current Levonelle SmPC. As highlighted above, the contraceptive efficacy of LNG EHC diminishes with time since unprotected intercourse. A narrower window of use would be expected to improve contraceptive efficacy but data are not available to allow direct comparison with the lower doses of these studies.

The studies by He et al. (1990, 1991) and Kesseru et al. (1973) also both allowed or required that repeat dosing of LNG was used following subsequent acts of unprotected intercourse within the same (monthly) cycle. The MAH has attempted to address the concern that repeated dosing may resemble standard (daily) progestogen-only oral contraception rather than EHC use by looking at the data from Kesseru et al. (1973) for women who had used <5 pills per month from groups 300-350-400 mcg (i.e. maximum 1200 to 1600 mcg LNG per month). Although this would represent a total intake similar to Levonelle it does not address the contraceptive efficacy of using lower doses when LNG is used in a manner that resembles the currently licensed posology of a single dose as closely as possible.

2.3. Clinical safety

Adverse drug reaction reports

During the covered period overall 35,886 individual case safety reports (ICSRs) including 67,115 adverse drug reactions (ADRs) were received by the MAHs Pharmacovigilance Department in connection with the LNG EHC.

In the Safety Database altogether 3008 cases of lack of efficacy (LOE) (representing 8.4% of all ICSRs) were reported since the date of first authorisation of the product. Five hundred and ninety one cases were medically confirmed (19.6%) and 2417 were medically unconfirmed (80.3%). 561 cases of the 3008 ICSRs related to LOE (18.6%) were received from the MSs involved in the procedure. One hundred and sixteen reports from the 561 LOE cases (20.9%) collected from the MSs contain other medicines besides the LNG EHC. These medicines were specified as other suspect, concomitant or interacting drug in these reports.

The MAH screened the ICSRs for enzyme inducers listed in the SmPC for LNG EHC, including efavirenz. Active ingredients of barbiturates were selected based on the Anatomical Therapeutic Chemical (ATC) classification system. Griseofulvin was excluded as the enzyme-inducing activity was determined from studies in rats that have not been confirmed in human studies.

Overall seven LOE cases were identified in the Company's safety database, which comprise enzyme-inducers in addition to the MAH's LNG EHC. Five cases were received from the United Kingdom between 2000 and 2005 and all were medically confirmed. The suspected interacting medicines were Hypericum perforatum in four cases and carbamazepine in one case. The other two ICSRs (1 each from the USA and New Zealand) reported Hypericum perforatum as the suspected interacting substance; neither of these cases was medically confirmed. No LOE cases were received in connection with efavirenz.

The five LOE cases with LNG EHC and enzyme-inducer combination of the total 3008 LOE reports (representing 0.17%) in the MAH's Safety Database do not refer to any potential safety issue.

Although there are few ADR reports of contraceptive failure during concomitant use of enzyme inducers with LNG EHC and none with efavirenz specifically, this may be due to under reporting due to an expectation of lower efficacy compared to other contraceptives. According to the latest PSUR, from the first marketing authorisation approval to December 2014, approximately 452,157,395 patients worldwide were exposed to the single dose of formulations of LNG 1500mcg. With best case efficacy of

95% when LNG is taken within 24 hours of unprotected sexual intercourse (UPSI), an excess of 22 million cases of contraceptive failure might have been expected from this widespread use. This is far in excess of the 3008 cases of loss of efficacy reported to the MAH.

Nevertheless a consistent pattern emerges of reduced contraceptive control, either in terms of breakthrough bleeding or ovulation, or pregnancies noted with reduced plasma LNG levels during concomitant use of enzyme-inducers. Notably, there were three unintended pregnancies amongst 20 efavirenz users in a 48 week study with LNG implants and none amongst the nevirapine users (n=20), who had higher LNG levels than either the EFV users or the control group. In addition, the MAH has six post-marketing reports on their database of contraceptive failure with St John's wort, another enzyme inducer.

For non-emergency forms of LNG-containing contraception, the decreased efficacy resulting in an increased risk of pregnancy is recognised in clinical guidance and in the SmPCs of hormonal contraceptives with advice to use additional or alternative contraception.

3. Consultation with patients, consumers and healthcare professionals

Consultation with patients and consumers and with relevant healthcare professionals including community pharmacists, nurse practitioners, general medical practitioners, and clinical specialists in gynaecology, HIV/AIDs and epilepsy across the EU took place during the referral assessment period. The patients and consumers were asked to give their views on the proposed wording to be included on the outer carton and in the package leaflet. A summary of the conclusions is provided below.

3.1. Consultation with patients and consumers

Overall the respondents correctly identified from the outer carton label which situations qualified for using a double dose or would opt to speak to a pharmacist or doctor. Likewise the respondents correctly identified from the package leaflet which situations qualified for using a double dose, even if they opted not to follow the instructions. In addition, the majority of the respondents correctly identified when to take a single dose, without the need to consult a healthcare professional.

There was however ambiguity over whether and when a healthcare professional should be consulted if a double dose was applicable. The CHMP discussions concluded that a double dose could be taken without prior consultation with a healthcare professional.

3.2. Consultation with healthcare professionals

Overall the respondents found the proposed outer carton label and package leaflet text to be clear, though some questioned whether a double dose would be effective. Several of the responses appear to reflect the current national and clinical practices of the respondents which is of special interest. They do highlight a generally low level of awareness regarding interactions of enzyme inducers with emergency contraception compared to routine contraception.

4. Discussion and overall conclusions

Levonorgestrel (LNG)-containing products are authorised in the European Union (EU) as emergency hormonal contraceptives (EHC).

The CHMP was requested to give its opinion on whether a double dose of Levonelle 1500mcg would be a suitable form of emergency contraception for patients taking concomitantly enzyme inducers mainly CYP3A4 enzyme inducers after unprotected intercourse or failure of a contraceptive method, in women who are unwilling or unable to use non-hormonal methods, such as a copper-based intra-uterine device (Cu IUD).

The CHMP reviewed all data available from clinical studies, published literature, post-marketing experience, including responses submitted by the MAH in writing, as well as the results of a written consultation with patients and consumers, and healthcare professionals across the EU. A relevant summary of the conclusions is presented below.

(i) Reduction in plasma levels with efavirenz and other enzyme inducers

The study of Carten et al. (2012), used a cross-over design, a clinically relevant dose of efavirenz and the size was reasonable for a drug-drug interaction (DDI) study. Despite some variabilities overall, the data show consistent and marked reduction by about half of the plasma LNG levels during concomitant administration of efavirenz, with decreases in LNG AUC_{0-12} of >40% observed in 90% of the women. In addition, plasma LNG levels were lower by a similar magnitude when LNG was administered via contraceptive implants in efavirenz users compared to HIV-positive women not yet in need of anti-retroviral therapy. Taken together, this suggests that the magnitude of the efavirenz effect has been reliably estimated by Carten et al. (2012).

The relevance of the divided dosing used by Carten et al. (2012) for the currently licensed single dose LNG was raised. Limited data with a 6mg dose of LNG shows higher Cmax than seen with 1.5mg, suggesting that saturation of LNG uptake does not occur at the standard EHC dose. Secondly, AUC, the main measure of exposure, has generally been found (Johansson et al 2002) to be dose-proportional. Finally, the dosing regimen used by Carten et al. (2012) was the previously approved posology for Levonelle, which was amended to a single 1500mcg dose following demonstration that the $AUC_{0-\infty}$ resulted in identical exposure and that there were no differences between the effectiveness or safety of LNG 2 x 750 mcg tablets (12 hour interval) and LNG 1500 mcg tablet administered as a single dose.

Therefore the CHMP is of the opinion that the findings of Carten et al. (2012) should apply equally to LNG EHC when it is taken as a single 1500mcg dose.

Specific data for interactions of other enzyme-inducers with EHC doses of LNG are not currently available. However studies following after 14 days treatment with St John's wort found similar >50% decreases in AUC for midazolam or alprazolam used as probes for CYP3A4 activity. Also, decreases in exposure of the LNG component of combined hormonal contraceptives have been noted with several enzyme inducers: LNG AUC was reduced by 36 to 47% reductions with oxcarbazepine; 40 to 46% with carbamazepine; 42% with phenytoin; 37% with eslicarbazepine; and 40% with perampanel.

(ii) Clinical significance of reduced plasma LNG levels

The CHMP acknowledged the limited clinical data regarding lack of efficacy of LNG-containing contraceptives with concomitant use of CYP3A4 enzyme inducers by which to judge the clinical significance of reduced plasma LNG levels during EHC.

There are also limited data on whether lower levels of LNG may be effective for EHC. One small study (n=58 women using cross-over design) found comparable efficacy of 750 and 1500mcg LNG using disruption of ovulation as an endpoint (Croxatto et al., 2004) when LNG was taken in the follicular phase, i.e. prior to ovulation.

Two parallel group studies examined contraceptive efficacy with lower doses of LNG: one study with 361 women observed similar crude pregnancy rates when LNG tablets were taken 8 hours after unprotected sexual intercourse (UPSI) using two formulations of 750mcg LNG tablets which were not bioequivalent. A second study looked at the contraceptive efficacy of LNG doses up to 400mcg, taken 3hours after UPSI by 4631 women in total. Exposure to 400mcg LNG represented the largest group, with 2801 patients studied, 71% for >6 months and 48% for > 12 months. There were 75 pregnancies in the 400mcg LNG treated group, yielding a failure rate of 3.52% and a method failure rate of 1.69%. The currently licensed dose of 1500mcg was not included in either of the contraceptive efficacy studies, so direct comparison of efficacy is not possible. Notably both contraceptive efficacy studies mentioned here required or allowed repeat use of LNG during the cycle and these studies examined contraceptive efficacy when LNG was used within 3 or 8 hours after UPSI and not when it used according to the current regimen, that is, within 72 hours of UPSI. This is important as contraceptive efficacy of LNG EHC diminishes with time since UPSI: from 95% within 24 hours to 58% if started between 48 and 72 hours. Currently the minimally effective dose for LNG EHC is not known.

Moreover, when other forms of LNG-containing contraception are considered, a consistent pattern emerges of reduced contraceptive control being seen, either in terms of breakthrough bleeding or ovulation, or pregnancies noted with reduced plasma LNG levels during concomitant use of enzyme inducers. Notably, there were 3 unintended pregnancies amongst efavirenz users in a 48 week study with LNG implants and the MAH has 6 post-marketing reports on their database of contraceptive failure with St John's wort, another enzyme inducer.

Although there are few adverse drug reaction (ADR) reports of contraceptive failure during concomitant use of enzyme inducers with LNG EHC, and none with efavirenz specifically, this is likely linked to significant under-reporting for loss of efficacy in general when expected contraceptive failure rates and widespread use of LNG EHC are considered. The reasons for the under-reporting are not known but may be due to an expectation of lower efficacy compared to other contraceptives.

For non-emergency forms of LNG-containing contraception, the decreased efficacy resulting from reduced plasma levels are considered to lead to in an increased risk of pregnancy. This is recognised in clinical guidance and in the product information of hormonal contraceptives which advise use of additional or alternative contraception.

The CHMP agreed that plasma exposure levels of LNG vary between women, but data from studies with combined hormonal contraceptives have indicated that plasma LNG levels are consistently reduced by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. The recent study with LNG-containing emergency contraception (Carten et al., 2012) showed that concomitant administration of efavirenz reduces plasma levels of LNG (AUC) by around 50%. The minimally effective dose of LNG for emergency contraception has not been established, but it is important to preserve efficacy margins for contraception in users of enzyme inducers.

(iii) Management options – Dose increase / alternative treatment

Currently the SmPC and PL for Levonelle 1500mcg and associated names list a number of enzyme inducers which may affect contraceptive efficacy but do not provide any information on the magnitude of the effect or advice on appropriate management of the interaction, other than for the woman to tell her doctor. Specialist clinics are not necessarily aware of the importance of the interactions and women rely on specialist clinical advice. Therefore the CHMP recommended that clear SmPC advice on managing these interactions is needed for all potential EHC providers.

The SmPCs for regular contraception products containing LNG advise using additional or alternative methods of contraception, depending on the duration of use of the enzyme inducer.

It is accepted that a woman using an enzyme inducer would ideally use a method that is unaffected by the interaction; indeed such women would be unlikely to need EHC. However this may not be realistic in all situations. Currently two other forms of emergency contraception are available, ulipristal acetate and Cu-IUDs. The product information for ulipristal acetate advises to avoid use with concurrent enzyme inducers due to enhanced metabolism. Fitting a Cu-IUD is a skilled procedure and this option may not be available, suitable or acceptable for all women. Moreover, to access this, a woman needs first to be aware of the risks associated with medicines interacting with LNG. Thus the CHMP concluded that there is a need for timely and clear advice for clinically relevant interactions.

Part of this advice to women is for a dose adjustment to counteract reduced plasma LNG levels when EFV and the other enzyme inducing medicines are used. From the data available it was proposed the use of a double dose of LNG EHC during and for 4 weeks after cessation of treatment with any enzyme inducers currently listed in the SmPC for this product. On this basis a double dose of LNG EHC for EFV users and all other enzyme inducers is recommended. Cu-IUDs can be used up to 5 days following UPSI but this may not be an option for all women on medical grounds (e.g. following recent expulsion or perforation, recurrent vaginal infections, and increased risk of bleeding is undesirable for female HIV patients), due to access issues (lack of availability of appropriately skilled HCPs) or due to personal choice (e.g. for women not in long term relationships at the time of UPSI). Finally the decision on whether a Cu-IUD is appropriate or not for a woman should be a clinical decision that considers her individual circumstances.

The CHMP considered the possibility that a double dose may not be adequate to fully compensate the effects of strong enzyme inducers. Although this possibility does exist, a double dose would still result in higher plasma LNG levels than under the current posology and thus reduce the risk of contraceptive failure. Interestingly, a recent publication of a small PK study in obese women vs normal BMI women (Edelman et al., Contraception, 2016, in press) found that C_{max} and $AUC_{(0\text{-}2.5h)}$ of total LNG was doubled when a double dose of LNG EHC (3000mcg LNG) was used. Although this study was not in association with enzyme inducers, it suggests that linearity of C_{max} is maintained up to 3mg LNG.

Conversely, a double dose may over compensate the effects of less strong enzyme inducers. However in this case, the exposure to LNG would be less than that for a woman taking a double dose (i.e. 3 mg LNG) whilst not using a concomitant enzyme inducer. Non-clinical data, a prospective cohort study investigating human pregnancy outcomes after LNG EHC failure, and data from post-marketing reports of overdose all suggest that overdosing (on a one-off or occasional basis) does not cause severe adverse reactions and no new safety concerns were raised. Thus safety concerns related to the over compensation of less strong enzyme inducers would also seem unlikely.

In conclusion, the CHMP agreed that whilst the use of a Cu-IUD may be the preferred option for emergency contraception for use with all enzyme inducers, recommending a double dose of LNG EHC represents a pragmatic management option, with no significant known safety issues, to reduce the risk of contraceptive failure for women unable or unwilling to use a Cu-IUD. The SmPC and PL text amendments proposed address appropriately all concerns.

(iv) Communication to healthcare professional and patients on double dosing for EHC management

Concerns have been raised by the CHMP of potential for medication errors related to non-prescription supply (i.e. targeted patients not using the double dosing as unaware). There is a need to educate healthcare professionals and patients about the interaction concerns and the related recommendations. It is considered that specific training is not needed for healthcare professionals, rather a Dear healthcare professional communication (DHPC) should be issued to highlight the change in prescribing advice. In this respect, the CHMP recommended that the national competent authorities (NCAs) should

outline the amendments to the SmPC and the reasons for the change through their normal means of communication with healthcare professionals.

In addition, the CHMP considered that instructions for an amended dose for users of enzyme inducers should be part of the package leaflet and should also be highlighted on the product outer carton labelling as the information should be available prior or during the purchase of the medicinal products to get the appropriate number of packs. In that regards, the CHMP recommended that to improve the delivery of the information, the effect of the enzyme inducers should be included directly after the usual dosage instructions on the same side of the carton.

In that way the CHMP wanted to ensure that the instructions on dosing are as clear as possible on the outer carton labelling and the package leaflet, in order to maintain the non-prescription supply without increasing the risk of medication errors. In order to assess the effectiveness and readability of this advice in the product information, a consultation was undertaken with patient and consumer groups and relevant healthcare professionals, with responses from across the EU. This showed that the majority of potential users could correctly identify from the information provided when it would be appropriate to use a single dose and when it would be appropriate to use a double dose, due to concomitant or recent use of interacting medicines or would seek advice from a healthcare professional. The responses also highlighted a low level of awareness of interactions with LNG EHC, underlining the need for proactive national communications on the outcome of the present review. For that reason the CHMP has discussed the key elements for communication to healthcare professionals and patients to facilitate the communication at national level.

In addition as the scientific conclusions of this assessment apply as well to the 750mcg LNG-containing medicinal products indicated in emergency contraception, the MAHs should take note of this recommendation and apply the scientific conclusions to those products accordingly.

To the extent that other 750mcg and 1500mcg LNG-containing medicinal products indicated in emergency contraception not included in this assessment but are currently authorised in the EU, or are subject to future authorisation procedures by the Member States, the CHMP recommends that the concerned member states take due consideration of these scientific conclusions.

4.1. Overall benefit/risk assessment

The Committee concluded that the benefit-risk balance of Levonelle 1500mcg and associated medicinal products remains favourable, subject to the warnings and changes to the product information agreed.

5. Risk minimisation activities

5.1. Amendments to the product information

The CHMP considered that amendments to sections 4.2 and 4.5 of the SmPC, Labelling and PL were necessary.

A. Summary of Product Characteristics

Section 4.2 Posology and method of administration

Women seeking LNG emergency contraception who have used enzyme-inducing medicines or herbal medicines during the preceding 4 weeks should use a non-hormonal EC or if that is not a suitable or available option, the usual dose of LNG should be doubled.

Section 4.5 Interaction with other medicinal products and other forms of interaction

Information was added on the reduced plasma levels of LNG when it is administered concomitantly with efavirenz. In addition, the advice mentioned in section 4.2 should also be inserted in this section.

B. Labelling

In order to ensure the correct use of Levonelle, advice on when to take a double dose was included on the medicine's outer carton. This advice should be located after and on the same side of the carton as the usual dosage information.

C. Package Leaflet

The Package Leaflet has been updated to include the information on the interaction of efavirenz and other enzyme inducers when administered concomitantly with LNG.

5.2. Communication plan

The CHMP agreed that for Levonelle and associated names and in view of the public interest on the issue assessed, the national competent authorities of the MSs may decide to communicate on the outcome of this review at national level, owing to the differences' in each national system and the legal status of each product (Levonelle and associated names is a prescription medicine in some MSs or distributed over-the-counter (OTC) in others).

6. Grounds for Recommendation

Whereas,

- The Committee considered the referral under Article 13(2) of Regulation No 1234/2008.
- The Committee reviewed all available data from clinical studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holder (MAH), in support of the efficacy and the safety of Levonelle 1500mcg and associated names in relation to the interaction with efavirenz. Furthermore the Committee discussed data regarding other hepatic enzyme inducers including barbiturates and other medicines to treat epilepsy, medicines used to treat tuberculosis like rifampicin and herbal medicines containing Saint John's wort.
- The Committee took also into account written consultations of consumers, patients and healthcare professionals before recommending the agreed changes to the product information.
- The CHMP concluded that in view of the available data for Levonelle 1500mcg and associated names, information should be available on the effect of efavirenz and other hepatic enzyme inducers when taken concomitantly, or for 4 weeks after cessation of treatment with all enzyme inducers. In particular in order to manage the effect of this interaction, the amendments to the product information include the recommendation of double dose adjustment of Levonelle 1500mcg and associated names when a Cu-IUD is not suitable or available.

In view of the above, the Committee considers that the benefit-risk balance of Levonelle 1500mcg and associated names remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Levonelle 1500mcg and associated names.

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