Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

NorLevo® / Vikela® / PiDaNa® Levonorgestrel

UK/W/0087/pdWS/001

Marketing Authorisation Holder: HRA Pharma

Rapporteur:	UK
Finalisation procedure (day 120):	18 January 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	NorLevo® / Vikela® / PiDaNa®
INN (or common name) of the active substance:	Levonorgestrel
MAH:	HRA Pharma
Currently approved Indication:	Emergency contraception within 72 hours after an unprotected sexual intercourse or in case of failure of a contraceptive method.
Pharmaco-therapeutic group (ATC Code):	G03AD01
Pharmaceutical form and strengths:	Tablet 0.75 mg / 1.5 mg

I. EXECUTIVE SUMMARY

This is a data submission for levonorgestrel in accordance with Article 46 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The UK is the rapporteur for this procedure.

One MAH has submitted a paediatric study that was completed after January 2007 (Study number NO-EPI-002-2008).This was a prospective observational study concerning the use and efficacy of levonorgestrel emergency contraception pills in family planning centres in France. The study included 579 women with a mean age of 19 years; half of the participants were less than 18 years of age. Adolescents were found to have a comparable failure rate (2.6%) as adult women (2.0%) in this study.

In addition, the MAH stated that data from literature, from clinical studies including levonorgestrel and from post-marketing pharmacovigilance do not show specific signals in the paediatric population.

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 46, the benefit-risk balance of levonorgestrel emergency contraception pills remains unchanged.

II. RECOMMENDATION

Based on the review of the submitted paediatric data, the rapporteur recommends the following updates in SmPC and PL for levonorgestrel emergency contraception pills:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]

Paediatric population
There is no relevant use of <product name> for children of prepubertal age in the indication emergency contraception.

Section 5.1 Pharmacodynamic properties

[This section should be amended to include the below wording]

[…]

Paediatric population
A prospective observational study showed that out of 305 treatments with levonorgestrel emergency contraceptive tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

PACKAGE LEAFLET

1. WHAT <product name> IS AND WHAT IT IS USED FOR

[This section should be amended to include the below wording]

[…]

When should emergency contraception be used?

[…]

<Product name> is not indicated for use before the first menstrual bleeding (menarche).

III. INTRODUCTION

On 6 March 2015, the MAH submitted a completed paediatric study for levonorgestrel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH also submitted the following documentation:
- Short critical expert overview
- Line listing
- Levonorgestrel product information [Summary of Product Characteristics (SmPC) / Package Leaflet (PL)] currently approved in some EU member states
- Periodic Safety Update Reports (PSURs) covering periods 17 April 2010 to 16 April 2011, 17 April 2009 to 16 April 2010 and 17 April 2008 to 16 April 2009.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

NorLevo® / Vikela® / PiDaNa®
NorLevo® / Vikela® / PiDaNa® are tablets containing either 0.75 mg or 1.5 mg levonorgestrel (LNG).

The currently approved SmPC of NorLevo® has the following information:

4.1 Therapeutic indication
Emergency contraception within 72 hours after an unprotected sexual intercourse or in case of failure of a contraceptive method.

4.2 Posology and method of administration
Oral use
The treatment necessitates the intake of two 0.75 mg tablets or of one 1.5 mg tablet in a single administration. The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. The tablets must be taken as soon as possible, preferably within 12 hours after the unprotected intercourse, and no longer than 72 hours (3 days) after the intercourse.

Licensing status:
Licensing status of NorLevo® / Vikela® / PiDaNa® in some EU countries was provided by the MAH. Additionally, the MAH reported that in Europe, LNG emergency contraception pills are available in all countries aside from Malta, and are generally available without prescription.

NorLevo® / Vikela® / PiDaNa® tablets are not licensed in the UK. LNG emergency contraception pills are licensed in the UK under other various product names. They are available as prescription only medicines or over-the-counter medicines.

IV.2 Clinical aspects

1. Introduction
For study NO-EPI-002-2008, the MAH has submitted the Final study report (in French) and an abstract (in English).

2. Clinical study NO-EPI-002-2008

Study title:
Use and efficacy of emergency contraception in France: Prospective observational study in Family Planning Centres of Val de Marne in pharmacies

Abstract
The investigators report the results of a prospective observational study of the dispensation of emergency contraceptive pills in 25 family planning centres in the Val de Marne region close to Paris. Women who requested emergency contraception in a participating family planning centre were invited to participate in the study. The study consisted of three face-to-face interviews, the first at the time of emergency contraception dispensation, the second approximately one month later, and the third four to six months later.

Of the 579 women invited to participate in the study, 409 women consented and entered the study for a total of 432 emergency contraception treatments (women were allowed to participate in the study on multiple occasions). Their mean age was 19 (range 14-52), they tended be single (86%) and not have children (86%). Half of the women in the population were less than 18 years old. They purchased an emergency contraception product following intercourse without contraception (44%) or a contraceptive accident (broken condom for 23%, missed pill for 12%). Fewer than half (40%) of the participants had already taken an emergency contraceptive pill at least once in the past. Levonorgestrel-only emergency contraception was administered to all of the participants by family planning staff as two 0.75 mg tablets administered in a single intake.

The second interview took place approximately one month after the first, with a total of 287 women successfully contacted, corresponding to 305 emergency contraception treatments. Seven women reported having become pregnant after taking emergency contraception, resulting in an overall failure rate of 2.3%. There was no difference in failure rate between women under 18 (4/153 or 2.6%) and women 18 and over (3/152 or 2.0%). For the other women, their menstrual period following emergency contraception intake occurred earlier than expected for 33% and later than expected for 24%.

The third questionnaire was completed three to six months after the first by 151 women (corresponding to 164 emergency contraception treatments). The majority of the respondents (92%) reported both being sexually active and using a method of contraception (94%) at the time of the interview, with a marked increase in the use of oral contraception and male condoms compared to at the time of enrolment in the study.

Rapporteur's comments:

This prospective observational study provided some insight into the use of emergency contraception pills in adolescents. Half of the study population who were given LNG-EC pills was less than 18 years old, showing noteworthy use in adolescents.

The information relevant to the paediatric population that transpired from this study is the failure rate in adolescents which was found to be 2.6%. This was comparable to the failure rate in adults which was 2.0%.

Failure (pregnancy) rate of levonorgestrel emergency contraception pills has also been described in a phase III trial and meta-analysis comparing two emergency contraceptive pills: ulipristal acetate or levonorgestrel (Glacier *et al.* 2010).

Forty-nine girls under 18 years old, comprising 4% of the studied population, were included in the phase III trial. Overall, pregnancy occurred in 2.6% of those who were randomised to receive LNG following unprotected intercourse.

The results of the Phase III trial and meta-analysis are also tabulated in the Faculty of Sexual & Reproductive Healthcare Clinical Guidance on Emergency Contraception (updated January 2012). The table from this clinical guidance is provided below:

Table 3 Results of randomised trials and meta-analysis of ulipristal acetate versus levonorgestrel[a]

Authors	Design	Time since UPSI (hours)	Ulipristal acetate			Levonorgestrel			OR (95% CI)	p
			Exposed (n)	Pregnancies (n)	Rate (%)	Exposed (n)	Pregnancies (n)	Rate (%)		
Creinin *et al.*[53]	Phase II randomised non-inferiority trial	0–72	773	7	0.9	773	13	1.7	0.50 (0.18–1.24)	0.135 NS
Glasier *et al.*[57]	Phase III randomised non-inferiority trial	0–120	941	15	1.6	958	25	2.6	0.57 (0.29–1.09)	0.091 NS
Glasier *et al.*[57]	Meta-analysis	0–24	584	5	0.9	600	15	2.5	0.35 (0.11–0.93)	0.035
		0–72	1617	22	1.4	1625	35	2.2	0.58 (0.33–0.99)	0.046
		0–120	1714	22	1.3	1731	38	2.2	0.55 (0.32–0.93)	0.025

[a]In the meta-analysis the efficacy-evaluable population excluded women aged older than 35 years as recommended by the US Food and Drug Administration, therefore subject numbers may differ from the original papers.
CI, confidence interval; NS, no significant difference; OR, odds ratio; UPSI, unprotected sexual intercourse.

The rapporteur is of the view that the failure rate of levonorgestrel EC pills in the adolescent group, as reported in the prospective observational study, is comparable to the failure rate described in the above phase III trial, meta-analysis and in current clinical guidance. It is therefore recommended that this information is added to the SmPC and PL of LNG-EC pills.

Post-marketing safety

The MAH stated that overall, the analysis of the cases collected during the period covered by the last Periodic Safety Updated Report (PSUR) submitted in EU (period 17/04/2008 to 16/04/2011) does not change the safety profile of Norlevo®.

In addition, the MAH reported that safety monitoring through pharmacovigilance activities has not revealed new signals associated with LNG emergency contraceptive use.

Rapporteur's comments:

The rapporteur notes that the conclusion from the three submitted PSURs was that:
'The benefit/risk ratio of Norlevo® remains favourable in the approved indication.'

Current product information
The MAH provided current product information (SmPC and PL) of levonorgestrel emergency contraception pills licensed in some EU member states.
The MAH stated that there is no restriction or specific information concerning the paediatric population (below 18 years old) except that LNG emergency contraception is only indicated in the post-menarchal population.
No change to SmPC and PL has been proposed by the MAH.

Rapporteur's comments:
The guideline on Summary of Product Characteristics (September 2009) states that: *'if there is no indication for the product in some or all subsets of the paediatric population, no posology recommendation can be made, but available information should be summarised using one or a combination of standard statements as appropriate'*. Of note, standard statements in this regard are provided in the SmPC guideline.
Given that emergency contraception is not indicated in the pre-menarchal population, the Rapporteur recommends that the following statement is added in section 4.2 of SmPC:

'There is no relevant indication for the use of <product name> before menarche.'

V. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 89

- **Overall conclusion**

Based on the submitted data, the rapporteur considers that the benefit-risk balance of levonorgestrel emergency contraception pills remains unchanged.

- **Recommendation**

It is noted that the submitted paediatric study provides information on the failure rate of levonorgestrel emergency contraception (LNG-EC) pills in adolescents. Therefore, the rapporteur recommends that this information is added to the product information of LNG-EC pills.
Additionally, in line with the Guideline on SmPC (September 2009), the rapporteur proposes that a statement is added in section 4.2 to reflect that there is no indication in the pre-pubertal population.

SmPC changes are recommended in sections 4.2 and 5.1 as follows:

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]
Paediatric population
There is no relevant indication for the use of <product name> before menarche.

Section 5.1 Pharmacodynamic properties

[This section should be amended to include the below wording]

[…]
Paediatric population
A prospective observational study showed that out of 305 emergency contraception treatments with levonorgestrel tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

- The MAH is requested to comment on the SmPC updates as proposed by the rapporteur (see Section V).
- In accordance with the SmPC updates, the MAH is requested to provide a proposal for Package Leaflet (PL) wording.

VII. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

Question 1:
The MAH is requested to comment on the SmPC updates as proposed by the rapporteur (see Section V).

MAH response:
1. The MAH agrees with the Rapporteur's Preliminary Assessment Report to amend the SmPC with updates in Section 4.2 and Section 5.1 to address specifically to the paediatric population.
The MAH agrees to add the conclusions of the study of levonorgestrel on paediatric population in Section 5.1, with a slight update (editorial) in the wording. The texts proposed for deletion are in ~~strikethrough font~~, the proposed alternative texts are in **bold font.**
The MAH proposes the below wording:

> Section 5.1
> *[…]*
> *Paediatric population*
> A prospective observational study showed that out of 305 ~~emergency contraception treatments with levonorgestrel tablets~~ **treatments with levonorgestrel emergency contraceptive tablets**, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

Rapporteur's comments:
The MAH response is acceptable. Issue resolved.

2. Regarding Section 4.2, the MAH proposes to harmonise the wording for all emergency contraceptives (G03AD01 levonorgestrel 1.5 mg and G03AD02 ulipristal acetate 30 mg) and proposes the below wording:

> Section 4.2
> *[…]*
> *Paediatric population*
> There is no relevant ~~indication for the use of <product name> before menarche~~ **use of <product name> for children of prepubertal age in the indication emergency contraception.**
>
> **Adolescents: <product name> is suitable for any woman of child bearing age, including adolescents. No differences in safety or efficacy have been shown compared to adult women aged 18 and older (see section 5.1).**

Rapporteur's comments:
The wording 'There is no relevant use of <product name> for children of prepubertal age in the indication emergency contraception.' is accepted.

The new paragraph: 'Adolescents: <product name> is suitable for any woman of childbearing age, including adolescents. No differences in safety or efficacy have been shown compared to adult women aged 18 and older (see section 5.1).' is not accepted.

This paragraph affirms that in principle, the product may be used in all women of childbearing age (i.e. post-menarcheal female adolescents and adults). Although the submitted data during this work-sharing procedure provide some information on the use of levonorgestrel emergency contraception pills in adolescents, the data is not considered sufficient to substantiate a statement confirming that the product may be used in all women of childbearing age. Additionally, the submitted data in this paediatric worksharing procedure is not sufficient to assert that there are no differences in safety or efficacy between adult women and adolescents.

It should also be noted that Article 46 paediatric work-sharing procedure is not a basic harmonisation process (as per Recommendations on submission and assessment in paediatric worksharing, *Doc. Ref.: CMDh/141/2009/Rev2*). Harmonisation of the wording for all emergency contraceptives (including G03AD01 levonorgestrel 1.5 mg and G03AD02 ulipristal acetate 30 mg) is not within the scope of this procedure.

Based on the above comments, the addition of the new paragraph is not accepted as a recommendation of this paediatric work-sharing procedure.

3. The MAH proposes to include sub-chapters to the other paragraphs of the Section 4.2, with the below wording according to the QRD template:

Section 4.2
Posology
[…]
Paediatric population
[…]
Method of administration
[…]

Rapporteur's comments:
The MAH's proposal is acceptable.

Final SmPC wording for levonorgestrel emergency contraception pills:

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]
Paediatric population
There is no relevant use of <product name> for children of prepubertal age in the indication emergency contraception.

Section 5.1 Pharmacodynamic properties

[This section should be amended to include the below wording]

[…]
Paediatric population
A prospective observational study showed that out of 305 treatments with levonorgestrel emergency contraceptive tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

Question 2:
In accordance with the SmPC updates, the MAH is requested to provide a proposal for Package Leaflet (PL) wording.

MAH response:
The PL should be updated in accordance with the updates in the SmPC. The MAH proposes the below wording, as harmonised wording for all emergency contraceptives:

1. WHAT <product name> IS AND WHAT IT IS USED FOR
[…]

When should emergency contraception be used?
[…]
<Product name> is suitable for any woman of childbearing age, including adolescents.

Rapporteur's comments:
As discussed in the preceding comments for Question 1, the wording 'suitable for any woman of childbearing age' is not accepted.

In accordance with the final SmPC updates, the rapporteur recommends the following wording to be used in the PL:

1. WHAT <product name> IS AND WHAT IT IS USED FOR
[…]

When should emergency contraception be used?
[…]
<Product name> is not indicated for use before the first menstrual bleeding (menarche).

Final PL wording for levonorgestrel emergency contraception pills:

1. WHAT <product name> IS AND WHAT IT IS USED FOR

[This section should be amended to include the below wording]

[…]

When should emergency contraception be used?

[…]

<Product name> is not indicated for use before the first menstrual bleeding (menarche).

VIII. COMMENTS FROM MSS AT DAY 115

Following the circulation of the Day 90 PdAR, the rapporteur received comments from one member state that agrees with the conclusions of the assessment report and has no further comments.

IX. RAPPORTEUR'S FINAL CONCLUSION AND RECOMMENDATION

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 46, the benefit-risk balance of levonorgestrel emergency contraception pills remains unchanged.
Based on the review of the submitted paediatric data, the rapporteur recommends the following updates in SmPC and PL:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]
Paediatric population
There is no relevant use of <product name> for children of prepubertal age in the indication emergency contraception.

Section 5.1 Pharmacodynamic properties

[This section should be amended to include the below wording]

[…]
Paediatric population
A prospective observational study showed that out of 305 treatments with levonorgestrel emergency contraceptive tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

PACKAGE LEAFLET

1. WHAT <product name> IS AND WHAT IT IS USED FOR

[This section should be amended to include the below wording]

[…]

When should emergency contraception be used?

[…]

<Product name> is not indicated for use before the first menstrual bleeding (menarche).

The applicant is therefore requested to submit a Type IB variation to update the SmPCs and PLs of levonorgestrel emergency contraception pills in line with the above work-sharing recommendations within 60 days of this report.

X. REFERENCES:

A guideline on Summary of Product Characteristics (SmPC) – September 2009 by the European Commission. Available from:
http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[accessed 3 July 2015]

Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Emergency Contraception. Updated January 2012. Available from:
http://www.fsrh.org/pdfs/CEUguidanceEmergencyContraception11.pdf
[accessed 3 July 2015]

Glasier, A.F., Cameron, S.T., Fine, P.M. et al. (2010) Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 375(9714), 555-562.