UCB (Pharma) Ireland Limited
United Drug House, Magna Drive, Magna Business Park, Citywest Rd, Dublin 24, D24 X0CT

LEVETIRACETAM (KEPPRA®):

UPDATED DATA ON USE IN PREGNANCY

Dear Healthcare Professional,

UCB Pharma S.A., in agreement with the European Medicines Agency and the Health Products Regulatory Authority would like to inform you of the following:

Summary

- **A cumulative re-evaluation of data on pregnant women exposed to levetiracetam (Keppra®) monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) does not suggest an increase in the risk for major congenital malformations. These data are not sufficient, however, to completely exclude a teratogenic risk;**
- **Only limited evidence is currently available on the neurodevelopment of children exposed to levetiracetam (Keppra®) monotherapy *in utero*. However, available epidemiological studies (on about 100 children exposed *in utero*) do not suggest an increased risk of neurodevelopmental disorders or delays;**
- **Levetiracetam (Keppra®) treatment should always be reviewed by a specialist when a female patient with epilepsy is planning to become pregnant, and patients should be counselled on the known risks;**
- **If after careful assessment, treatment with levetiracetam (Keppra®) is considered clinically necessary during pregnancy, the following recommendations should be kept in mind when used during pregnancy:**
  - **the lowest effective dose is recommended;**
  - **when possible, monotherapy should be preferred because therapy with multiple antiepileptic drugs (AEDs) could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AED(s);**
  - **appropriate clinical management of pregnant women treated with levetiracetam (Keppra®) should be ensured, as physiological changes during pregnancy may decrease levetiracetam dose/plasma concentrations ratio (especially during the 3rd trimester);**
- **The Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for Keppra® (levetiracetam) have been updated to reflect the updated information.**

Background on the safety concern

Major Congenital Malformations (MCMs)

Some studies in animals have observed reproductive toxicity in association with levetiracetam exposure, though the overall evidence from the literature and from UCB-

sponsored non-clinical studies is not consistently suggestive of a teratogenic potential for levetiracetam in animals.

Clinical data from the literature, from prospective spontaneous reporting and from large pregnancy registries of AEDs (see below) found no evidence of an increased risk of the global rate of MCMs after exposure to levetiracetam monotherapy *in utero*. Still, none of these sources allow to completely exclude a teratogenic risk.

No clear conclusions could be drawn on the risk of MCMs with levetiracetam used in the context of polytherapy, as the pregnancy outcomes also depend on the other AED(s) to which levetiracetam is associated.

Registry data

Table 1 below shows the rates of MCMs associated with prenatal levetiracetam exposure across the different registries (North American Antiepileptic Drugs Pregnancy Registry [NAAPR], European Registry of AEDs and Pregnancy [EURAP], and UCB AED Pregnancy Registry), considering the prospectively followed pregnancies exposed to levetiracetam monotherapy, and the prospective pregnancy exposures to levetiracetam in combination with other AEDs (polytherapy):

Table 1: Levetiracetam MCMs rates across registries

	Monotherapy			**Polytherapy**		
Registry	Exposed pregnancies	MCM cases	MCM rates	Exposed pregnancies	MCM cases	MCM rates
EURAP[1]	599	17	2.8%	NA	NA	NA
NAAPR[2]	759	15	2.0%	485	11	2.3%
UCB AED Pregnancy Registry[3]	308	29	9.4%	135	17	12.6%

[1] From Tomson *et al* "Comparative risk of malformation with different antiepileptic drug treatments : EURAP, a prospective observational study"

[2] From May 2016 North American report including pregnancies with outcomes as of 01 Jan 2016

[3] Final study results with data as of 30 Apr 2016

Important methodological differences between the UCB AED Pregnancy Registry and both EURAP and NAAPR registries (including congenital malformation case definition, length of follow-up and differential reporting, and groups of pregnancies exposed to other AEDs available for internal comparisons) caused a large variability in the estimated rates of MCMs between registries. Indeed, applying the methodology for congenital malformation case

definition used in the EURAP and NAAPR registries would respectively exclude 43% and 80% of the cases identified as MCMs in the UCB AED Pregnancy Registry. Despite these methodological differences, none of these registries demonstrated significant evidence suggestive of an association between teratogenicity and prenatal exposure to levetiracetam.

Spontaneous reporting

As of 30 April 2016, 1185 cases of pregnancies exposed to levetiracetam were spontaneously and prospectively reported to UCB. Among the 423 cases for which the issue of the pregnancy was communicated to UCB and that resulted in live births, the following number of malformations were reported:

- Among 230 live births exposed *in utero* to levetiracetam monotherapy, there were 13 reported malformations (5.7%).
- Among 193 live births exposed in utero to levetiracetam in combination with other AEDs, there were 12 reported malformations (6.2%).

Interpretation of the post-marketing reports should be made with caution in view of the small proportion of cases with a known outcome, lack of control group, recall bias, barriers to reporting, and incomplete case documentation. The review of those pregnancy related individual case safety reports from the UCB safety database does not provide evidence of a causal link between levetiracetam exposure and MCMs.

Neurodevelopmental toxicity

Currently available data on the neurodevelopment of children exposed to levetiracetam *in utero* are limited. Only speculative conclusions (absence of reported neurodevelopmental disorders or delays) can be derived from the short follow-up of live births in the EURAP and NAAPR registries (12 months and 4 months respectively). In the UCB AED Pregnancy Registry, no significant neurodevelopment disorders/delays were found in children exposed to levetiracetam *in utero* and monitored up to 3 years of age. Publications from the literature mostly consists of 5 studies (3 with some patients overlap), analysing a total of 122 individual children exposed to levetiracetam monotherapy *in utero*, not all at the same age span. Still, none of the studies were suggestive of an increased neurodevelopmental risk in children exposed *in utero* to levetiracetam monotherapy. These limited data are, however, likely insufficient to exclude rare disorders.

Conclusion

A cumulative re-evaluation found no evidence of a safety signal for teratogenicity or neurodevelopmental toxicity associated with levetiracetam monotherapy. However, these data are not considered sufficient to completely exclude these risks. Levetiracetam (Keppra®) treatment should always be reviewed by a specialist when a female patient with epilepsy is planning to become pregnant, and patients should be counselled on the known risks. If it is considered clinically needed after careful assessment, levetiracetam (Keppra®) can be used during pregnancy. The lowest effective dose is recommended. When possible, monotherapy

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should be preferred because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AED(s).

Call for reporting

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 16764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie. Adverse events should also be reported to UCB (Pharma) Ireland Limited as listed below:

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Yours sincerely,

Dr Tim Aldwinckle 7th September 2018

Head of Medical and Business Integrity