UK Teratology Information Service
Regional Drug & Therapeutics Centre
16-17 Framlington Place
Newcastle upon Tyne
NE2 4AB

Clinical enquiries: 0344 892 0909
General enquiries: 0191 213 7880
Fax: 0191 261 8839
www.uktis.org

OFFICIAL UKTIS POSITION STATEMENT

Re: Update to the Librium® Summary of Product Characteristics (20th May 2022)

Background

On the 17th May 2022, an updated Summary of Product Characteristics (SPC) for Librium® (chlordiazepoxide) was published on the electronic Medicines Compendium website (see here). The updated SPC states, "*Due to the genotoxic potential of chlordiazepoxide, women of childbearing potential should use effective contraceptive measures while being treated with Librium and for 7 months following completion of treatment. If the patient suspects to be pregnant or intends to become pregnant, she should be warned to contact her physician to discuss discontinuation of Librium. Men are recommended to use effective contraceptive measures and to not father a child while receiving Librium and for 4 months following completion of treatment.*" Below is an official opinion statement from UKTIS regarding the updates to the Librium® SPC.

Summary

- **There are no newly published data on preconception chlordiazepoxide exposure in human pregnancy (maternal or paternal)**
- **The Librium® SPC updates are based on *in vivo* (animal) and *in vitro* studies (the details of which are not available)**
- **The SPC for Librium® indicates that not all the assays conducted indicated mutagenic effects**
- **The mutagenic potential for alternative benzodiazepines (diazepam, lorazepam and oxazepam) is unknown**
- **There is currently no evidence that preconception chlordiazepoxide use in humans is associated with mutagenic effects that impact fetal development**
- **Although there is currently no good evidence that chlordiazepoxide is teratogenic (following exposure in pregnancy), neonatal effects (including sedation/hypotonia and subsequent withdrawal) are an established risk associated with the late gestational benzodiazepine exposures**
- **It remains important that women (pregnant and non-pregnant) and men experiencing acute alcohol withdrawal are treated appropriately**
- **Fetal alcohol syndrome is a real and well-documented effect of consuming alcohol in pregnancy**
- **In contrast, the risks from chlordiazepoxide remain theoretical based on *in vitro/in vivo* studies with conflicting results, and importantly, no real-world human data substantiating the concerns**
- **Adequate treatment of alcohol dependency is likely to have a much greater benefit to health and wellbeing than the theoretical and unconfirmed risks suggested for chlordiazepoxide**
- **The available data suggesting mutagenic effects of chlordiazepoxide are not conclusive, and as such, the recommendations from the manufacturer are considered overly cautious, particularly when reflecting on the benefits of treating alcohol dependency and the risks from delirium tremens and seizures if chlordiazepoxide is withheld**

- **Clinicians should not be discouraged from using chlordiazepoxide based on this evidence**
- **The benefits of treating pregnant women (at any stage of pregnancy) experiencing acute alcohol withdrawal with chlordiazepoxide likely outweigh the risks**

Detail

After having conducted a review of the literature (20th May 2022), UKTIS confirm that there are no newly published data on human pregnancy (maternal or paternal) preconception exposure to chlordiazepoxide which relate to the updates in the Librium SPC.

As stated in the SPC (see here), women are being recommended to avoid pregnancy for 7 months and men to avoid fathering a child for 4 months after chlordiazepoxide treatment has ended based on the results of mutagenicity studies. Also as per the SPC, these mutagenicity studies have been conducted in animal and other assays (detail not in the SPC, but these other assays are generally bacterial or similar). However, it appears that the results of these mutagenicity studies are inconclusive, as the SPC states that not all the assays tested produced results indicative of mutagenic effects.

The *in vivo/vitro* mutagenic potential for alternative benzodiazepines (such as diazepam, lorazepam and oxazepam) is unknown.

There is currently no evidence that chlordiazepoxide use in either human females or males is associated with mutagenic effects that impact fetal development.

Published evidence regarding chlordiazepoxide use in pregnancy are limited, both quantitively and methodologically. Due to the indication of this medication, the available pregnancy exposure and outcome safety data are highly confounded (concomitant alcohol/substance misuse, socioeconomic status, smoking etc.). Although reports of malformations have been described, there does not appear to be a distinct pattern of anomalies. Therefore, there is currently no good evidence that chlordiazepoxide is teratogenic. Neonatal effects (including sedation/hypotonia and subsequent withdrawal) are a well-established risk associated with the use benzodiazepines in late pregnancy.

Fetal alcohol syndrome is a real and well-documented effect of consuming alcohol in pregnancy, whereas the risks from chlordiazepoxide have only been demonstrated *in vitro/in vivo* with conflicting results. Importantly, there are no real world human data which substantiate the concerns that chlordiazepoxide is either mutagenic or teratogenic. In contrast, alcohol is a proven human teratogen which can produce severe life-long neurodevelopmental impairments. Adequate treatment of alcohol dependency is therefore likely to have a much greater benefit to the health and wellbeing of women and men experiencing acute alcohol withdrawal, and their children, than the theoretical and unconfirmed risks posed by chlordiazepoxide.

Conclusion

It remains important that women and men experiencing acute alcohol withdrawal are treated appropriately. The available data suggesting mutagenic effects of chlordiazepoxide are not conclusive, and as such, the recommendations from the manufacturer are considered overly cautious, particularly when considering the benefits of treating alcohol dependency given the risks from delirium tremens and seizures if chlordiazepoxide is withheld. Clinicians should not be discouraged from using chlordiazepoxide based on the evidence communicated in the Librium SPC. The benefits of treating pregnant women (at any stage of pregnancy) who are experiencing acute alcohol withdrawal with chlordiazepoxide likely outweigh the risks.