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Citizen Petition Cover Letter

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition – request to re-label sodium containing N-Acetlycysteine Drugs to treat Acetaminophen Intoxication

To whom it may concern,
The undersigned ("petitioner") submits this petition in accordance with 21 CFR 10.30 to the US FDA. Specifically, we formally request that the FDA demands that products containing the sodium salt of N-Acetylcysteine and marketed for the treatment of Acetaminophen intoxication shall not only contain a warning for the general population about the high sodium content of the recommended therapeutic dose but also a Black Box Warning label for subjects considered "salt sensitive' and/or with preexisting cardiovascular or CNS disease according to 21 CFR 201.

We consider our request reasonable because the sodium dose administered to subjects with acetaminophen poisoning during the recommended treatment by far exceeds the upper limits defined by the USFDA.

Please contact us if you have any questions or require additional information.

Sincerely,

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June 18, 2024

Citizen Petition

The undersigned submits this petition under 21CFR Part 10.30 of the Federal Food, Drug, and Cosmetic Act. This petition requests an amendment to the labeling of sodium containing acetylcysteine products to include a statement regarding its use in patients sensitive to high sodium intake. A statement under "use in specific populations" was previously included in the CETYLEV (N-Acetylcysteine) effervescent tablets for oral solution) prescribing information, however, this statement has not been included in currently marketed drugs that use CETYLEV as the Reference Listed Drug (RLD) and contain sodium. Given the high sodium content in these products paired with the very large per-protocol-total-dose required to adequately treat the condition, the associated risks in normal patients and those sensitive to high sodium intake are crucial to be included in the Patient Information as a warning as specified under CFR 21.201.64. Moreover, a Black Box Warning should be considered for sodium sensitive subjects who require treatment with N-Acetylcysteine delivering high sodium amounts for Acetaminophen intoxication as detailed under 21CFR201.57.

A. Action Requested

We are requesting an amendment to the labeling of sodium containing acetylcysteine products to include a statement regarding the high sodium content in this product and a black label warning for its use in subjects with acquired or genetically caused salt sensitivity pertaining to possible deleterious cardiovascular- and possible central nervous system related serious adverse events. In addition, we are requesting a Black Box Warning for the "sodium sensitive population" and for subjects with pre-existing cardiovascular or CNS disease"

B. Statement of Grounds

Acute sodium load through medications with high sodium content has been found to lead to potentially deleterious cardiovascular (Perrin et al., 2017)(Peng et al., 2021) and/or neurological adverse events (Goshima et al., 2022) and have even been observed to cause fatalities at rather moderate dosages in both the pediatric and adult population (Campbell & Train, 2017). Serious adverse events following medication-driven high sodium loads are more likely to occur in the so-called "salt-sensitive" population, particularly in the non-hispanic black population (Schmidlin et al., 2007) but also occur in the general population. Acute sodium load not only exacerbates pre-existing arterial hypertension but can also elicit serious neurological adverse effects such as seizures and coma. Sodium loads observed to elicit such adverse effects have been identified for a series of acute and chronic medications (Perrin et al., 2017) (George et al., 2013).

In light of such observations, the FDA has published guidelines for labeling drug formulations with high sodium content (Drug labeling: sodium labeling for over-the-counter drugs: proposed amendment. Fed Regist 1991;56:1922). In addition, in 1994 the FDA have recommended:

> " that makers of prescription drugs declare the sodium content if it exceeds 5 mg (0.22 mmol) per single recommended dose and that they issue a warning if the sodium content exceeds 140 mg (6.09 mmol) per maximal daily dose" (Center for Drug Evaluation, and Research (US). *Approved drug products with therapeutic equivalence evaluations*. Commerce Clearing House.

It has come to our attention that one oral dosage form product that is approved for the treatment of acetaminophen intoxication contains high sodium and when administered according to the recommended administration scheme delivers large amounts of sodium within 36 hours. The total dose per administration scheme for a 70kg human subject amounts a total of 17.1g of sodium. (Ana Szarfman et al., 1995). Accordingly, the product CETYLEV, which is marketed for the treatment of acetaminophen poisoning has the following 'high sodium content" warning in its leaflet:

> *Patients Sensitive to High Sodium Intake*
> *CETYLEV tablets contain sodium. Consider the total sodium content from dietary and non-dietary sources in patients who may be sensitive to excess sodium intake, such as those with congestive heart failure, hypertension, or renal impairment.*
> *At the recommended dosage an average sized adult (60 kg) may receive a total of 7 grams of sodium (304.3 mEq) on the first day of treatment, 5.3 grams of sodium (230.4 mEq) on the second day of treatment, and 4.4 grams of sodium (191.3 mEq) on the third day of treatment.*

However, the marketed products for the treatment of acetaminophen intoxication surprisingly do not show such warning about their high sodium content with respect to the total dose administered during the recommended treatment regime neither in the leaflet nor on the label. Specifically, they provide no particular guidance to the physician nor the patient with respect to salt sensitive individuals and the general population. Moreover, no reference is being made to certain medical conditions such as cardiovascular disease, arterial hypertension, epilepsy and other CNS diseases or racial predispositions. We are highly concerned that albeit clear FDA regulations on the declaration of high sodium content of prescription drugs dosages for a given indication the marketed drugs for acetaminophen intoxication lack such "high sodium warning label" . In addition, given the various fatalities reported, particularly in salt-sensitive and/or pediatric population, a black label warning for the marketed product for this indication should be considered. The currently and formerly marketed products to treat acetaminophen intoxication are shown in Appendix 1. Furthermore, the high sodium warning label as recommended by the FDA for the Cetylev that served as the reference listed drug (RLD) for the marketed oral dosage

form products for this indication is provided in Appendix 2.

C. Environmental Impact

Not applicable

D. Economic Impact

Considering the relatively high frequency of medication associated high sodium load adverse effects, it can be concluded that the use of high sodium containing oral drugs, in an emergency, will add to the overall costs of treatment for acetaminophen intoxication. Such additional costs may be a prolongation of the hospital stay or required additional therapeutic measures due to adverse effects caused by the treatment associated with high sodium load.

Given the fact, that there is an alternative approved product in the US market i.e. Legubeti that does not contain sodium, we would like to make a case for a recommendation towards the preferential use of Legubeti, particularly in individuals with known cardiovascular disease and/or arterial hypertension.

E. Certification

The undersigned certifies that, to the best of knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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