Refusal Public Assessment Report for Human Medicinal Products

(Carbamazepine intravenous solution for Infusion)

1. Introduction:

Based on the review of safety & efficacy data
The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing Carbamazepine as Intravenous solution.

- The application for Carbamazepine intravenous solution is refused, as the submitted data fails to establish a compliant safety and efficacy profile"

2. Legal basis for application:

The application was submitted to the **Scientific Evaluation Unit for Pharmaceutical Products and Drug Development** in accordance to **Ministerial Decree 425/2015**

3. Scientific Overview:

3.1. Applied Scientific Information

3.1.1. Pharmacotherapeutic class

Anticonvulsants (antiepileptic drugs)

3.1.2. Therapeutic indication

The applicant has proposed the following therapeutic indications for Carbamazpine Intravenous solution:
indicated as replacement therapy for oral carbamazepine formulations, when oral administration is temporarily not feasible, in adults with the following seizure types (1):
• Partial seizures with complex symptomatology
• Generalized tonic-clonic seizures
• Mixed seizure patterns which include the above, or other partial or generalized seizures.

3.1.3. Therapeutic dose:

A replacement therapy for oral carbamazepine. Carbamazepine treatment should generally be initiated with an oral carbamazepine formulation.
The total daily dose is 70% of the total daily oral carbamazepine dose from which patients are being switched. The total daily dose should be equally divided in four 30-minute infusions, separated by 6 hours.
Patients should be switched back to oral carbamazepine administration at their previous total daily oral dose and frequency of administration as soon as clinically appropriate. The use for periods of more than 7 days has not been studied.

3.1.4. Warnings associated with the drug:

- Serious Dermatologic Reactions
- Aplastic Anemia and Agranulocytosis

3.1.5. Scientific Rational:

- Indicated as replacement therapy for oral carbamazepine formulations, when oral administration is temporarily not feasible, in adults.

3.2. Scientific Concerns:

Based on the review of available applied data for the submitted product, the following has been found:

- The applicant failed to demonstrate bioequivalence or adequate pharmacokinetic bridging between oral carbamazepine and the IV formulation.
- The applicant has not submitted adequate, recent, and scientifically evidence to support the safety and efficacy of Carbamazepine Intravenous solution in the proposed indication.
- The applicant failed to submit additive Therapeutic advantage for the availability of registered and marketed intravenous (IV) anti-epileptic alternatives in the Egyptian market for the same therapeutic indication.

4. Regulatory Status

By Searching in Reference countries approved by Technical committee of drug control it was found that:
The International regulatory status in the reference countries & scientific reference at the time of submission is as the following:
*No scientific references or reference countries are available for Carbamazepine as Intravenous solution.

Carbamazepine is authorized in scientific references & reference countries as immediate release tablets, extended release Tablets, chewable tablets, Suppositories & Oral suspension as follow:

****Carbamazepine immediate release Tablets 100,200,400 mg in countries such as:**
FDA, MHRA, Ireland, Sweden, Germany.
****Carbamazepine extended release Tablets 200,400 mg in:**
FDA, MHRA, Ireland, Canada, Germany, Sweden, Finland.
****Carbamazepine chewable tablets 200mg is available in:**
FDA, NDC, MHRA, Canada, PDR.
****Carbamazepine Suppositories 250mg, 125mg is available in:**
MHRA, Sweden, Norway.
****Carbamazepine Oral suspension 100mg/5ml is available in:**
TGA, FDA, MHRA, Ireland, Canada, Germany, Sweden, Finland.

5. Overall Conclusion & Recommendation:

Based on Scientific assessment of the applied medicinal product and submitted data by the applicant , the following conclusions were established as follow:

- **Insufficient Clinical Data:**
  The submitted data is not sufficient to support the efficacy or safety of Carbamazepine intravenous solution **where** clinical efficacy has not been established & the safety profile is not sufficiently characterized.
- **Absence of robust pharmacokinetic bridging data**
  The application lacks adequate pharmacokinetic bridging data to support bioequivalence or systemic comparability between intravenous and oral carbamazepine. Specifically:
  * The impact of bypassing gastrointestinal absorption and first-pass metabolism on carbamazepine pharmacokinetics were not adequately characterized.
  * lack of clinical safety and PK data evaluating how different infusion durations and rates impact peak plasma concentrations and acute toxicity.
- **No Additive Therapeutic Advantage:** No additional therapeutic benefit has been demonstrated that would justify the introduction of the proposed IV carbamazepine formulation over the currently available alternatives in the Egyptian market.
- **Narrow Therapeutic Index & Toxicity Risks:** carbamazepine is a **Narrow Therapeutic Index (NTI)** drug—where small shifts in plasma concentration can lead to either breakthrough seizures (loss of efficacy) or acute central nervous system toxicity &that requires robust proof of comparability before approving a parenteral route.
- **Excipient and Formulation Safety:** The poor chemical solubility of intravenous carbamazepine requires a heavy excipient burden (solubilizing agents/co-solvents). This introduces notable local tolerance risks—such as infusion-site reactions and phlebitis—as well as potential systemic hypersensitivity.
- **More research & studies are needed:** The application lacks robust clinical evidence demonstrating the efficacy, safety, and overall clinical benefit of the proposed intravenous formulation. The applicant has not demonstrated any added therapeutic value over the currently available treatment alternatives in the Egyptian market.
  Robust evidence derived from well-designed, adequately powered, randomized controlled clinical trials published in peer-reviewed scientific journals is required to confirm the safety, efficacy & and a favorable benefit–risk profile for submitted product.

Scientific Evaluation committee adopted a negative opinion regarding registration the products containing Carbamazepine as intravenous solution **.**

Technical Committee of Drug Control refused granting the marketing authorization for the medicinal products containing **Carbamazepine intravenous solution**

5. Final Decision:

Following a comprehensive evaluation of safety and efficacy, the Scientific Evaluation Committee and the Technical Committee for Drug Control have determined that the application for the medicinal product Carbamazepine Intravenous Solution lacks the necessary scientific justification and clinical validation to ensure a safe risk-benefit profile.

Accordingly, the Egyptian Drug Authority (EDA) issues a final rejection regarding marketing authorization for all products containing carbamazepine as intravenous Solutions