NATIONAL PHARMACEUTICAL REGULATORY DIVISION MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
ERDOMED® 300mg Hard Capsules (MAL20076014ARZ)
ERDOMED® 300mg Dispersible Tablets (MAL20076015ARZ)

ACTIVE INGREDIENT:
Erdosteine 300mg

PRODUCT REGISTRATION HOLDER:
Hyphens Pharma Sdn. Bhd.

PRODUCT MANUFACTURER:
Manufacturer & batch release: Edmond Pharma S.R.L, Italy
Primary & secondary packager: Lamp San Prospero S.p.A, Italy

APPROVAL DATE:
9th July 2020 (DCA 346)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

Mucolytic agent for use in adults with acute and chronic respiratory disorders associated with excessive mucus production.

1.2 Approved Posology

Elderly and adults above 18 years:
300 mg hard capsules: 1 capsule 2-3 times a day, for oral use.
300 mg dispersible tablets: 1 tablet 2-3 times a day, for oral use.

1.3 Method of administration

For oral use.

Method of administration for dispersible tablets

The tablets should be dissolved in a glass of water. The dispersion should be stirred with a spoon and drunk immediately. The score-line on the tablet does not divide the tablet into equal half-doses.

1.4 Pharmacological Aspects

Mechanism of action

Erdosteine, active ingredient of ERDOMED®, in addition to its mucolytic properties on bronchial mucus thus facilitating expectoration, shows effects in antagonizing the local formation of free radicals and inhibiting the activity of the elastase enzyme. Pharmacological studies have demonstrated that erdosteine does not possess these properties as such, but it is active only after metabolization. In fact, the SH groups, to which the activity is ascribed, are chemically used and become free only after metabolization or in alkaline environment. This property guarantees a good palatability with no bad taste and mercaptanic regurgitations and a good gastric tolerability.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Pharmaceutical Ingredient

- Overall the quality of API is in accordance with The International Council for Harmonisation (ICH) and WHO guidelines and have been assessed to meet the regulatory requirements.
- Erdosteine in the racemic form was consistently produced by the manufacturing process. The proposed starting materials have been adequately justified in line with ICH Q11 (Guideline on Development and Manufacturer of Drug Substance) and acceptable specifications have been set. The manufacturing process of Erdosteine was sufficiently described and adequate in-process controls are applied during the manufacturing process. Acceptable specifications and control methods for intermediates, starting materials and reagents have been presented.
- The characterisation of the API and its impurities are in accordance with the EMA Guideline on Chemistry of New Active Substances.
- The specification of API is controlled accordance to the in-house requirements. Batch analysis data for three batches were provided and the results were within the proposed specifications.
- The analytical methods used have been appropriately validated in accordance with the ICH Q2(R1) (Validation of Analytical Procedures: Text and Methodology) guidelines.
- The stability studies on three batches were performed for 6 months at 40˚C±2˚C/75%±5%RH and six batches were performed for 60 months at 25˚C/60%RH. The results of stability data showed that the API remains within the specification. The stability studies were conducted in accordance with ICH Q1 (Guideline on Stability Testing of New Dug Substances and Products).
- The proposed re-test period is 60 months, when store below 25˚C, packed in double polyethylene bags in a fiber drum.

2.1.2 Finished Product

- The manufacturing process has been validated and the results fulfilled the expected acceptance criteria proving that the finished product manufacturing processes are robust and reproducible.
- The stability studies data support a shelf life of 36 months when stored below 30°C. The available 36 months long term stability data at 30±2°C/75±5%RH and 6 months

accelerated stability data at 40±2°C/75± 5%RH remain well within specifications to support the shelf life.

- The products have passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- Certificate of GMP Compliance for the manufacturer was issued by the Italian Medicines Agency.

2.2 Efficacy

The evidence for the therapeutic efficacy and safety of erdosteine is based on a series of 22 randomised, double-blind, placebo and active-controlled trials in patients with stable chronic bronchitis and COPD, exacerbated COPD and ear, nose and throat (E.N.T.) diseases (such as acute, subacute and chronic exacerbated rhinopharyngitis, pharyngolaryngotracheitis and sinusitis). Representative studies are summarised below:

Table 1: Summary of Clinical Studies Conducted

Study type and design (n)	Objective(s)	Primary efficacy endpoint
The therapeutic efficacy of erdosteine in the treatment of chronic obstructive bronchitis: A meta-analysis of individual patient data. **[Cazzola M., *et al*. Pulmonary Pharmacology & Therapeutics, 2010]** 15 randomised, controlled trials focusing on the comparison between erdosteine and placebo or mucolytics Adults ≥18 years of age • medical history of chronic bronchitis, generally defined as the presence of cough and sputum production for at least 3 months in a year for over 2 consecutive years • acute exacerbation or stable CB/COPD n=1046 Treatment arms: i) Erdosteine 300mg capsule twice/thrice	To test the available evidence for the efficacy of erdosteine in adults with stable or exacerbated chronic bronchitis (CB)/ chronic obstructive pulmonary disease (COPD)	• Overall, erdosteine demonstrated improvement in the following outcome measures in comparison with comparators (both placebo and mucolytics): - Reduction in **cumulative global efficacy index (cGEI)** (-1.02; 95% CI -1.60, -0.44; p=0.0006). - Improvement in **cough frequency** (-0.19; 95% CI -0.34, -0.03; p=0.02). - Improvement in **cough intensity** (-0.30; 95% CI: -0.44, -0.17; p< 0.00001). - Improvement in **sputum viscosity** (-0.28; 95% CI: from -0.49, -0.07; p= 0.008). - Improvement in **expectoration** (-0.24; 95% CI: from -0.40, -0.08; p= 0.004). - Reduction in the presence of **catarrh rhonchi at auscultation** (-0.35; 95% CI -0.60, -0.10; p=0.006). • There was no significant difference in **sputum purulence** (-0.11; 95% CI: from -0.28, 0.07; p=0.25 and **dyspnoea** (-0.09; 95% CI -0.24, 0.07; p=0.29).

Study type and design (n)	Objective(s)	Primary efficacy endpoint
daily in addition to background therapy (antibiotics & bronchodilators) ii) Placebo or mucolytics (ambroxol, N-acetylcysteine, carbocysteine, sobrerol) with the same dosing schedules as erdosteine (i.e. twice/thrice daily) Treatment duration: 7-10 days		Conclusion: Treatment with erdosteine is associated with a significant benefit in terms of symptom improvement versus both placebo and mucolytics in patients with CB/COPD.
The effect of long term treatment with erdosteine on chronic obstructive pulmonary disease: The EQUALIFE Study [Moretti M. *et al.* Drugs Under Experimental and Clinical Research, 2004] Phase IV, double-blind, randomised, placebo-controlled, parallel-group, multicentre study Male and female patients aged 25-85 years old with a clinical diagnosis of COPD as defined by the European Respiratory Society (ERS) with ≥1 exacerbation during the winter preceding the study, a baseline FEV_1<70% of that predicted, an x-ray without evidence of acute lung diseases, current or past history of smoking >20pack/year, a stable condition at enrollment and at least 4 weeks since the last exacerbation. n=155 (25 - 85 years, mean age 67.5 years) Two treatment arms (Randomisation ratio 1:1): i) Erdosteine 300mg twice daily (n=79) ii) Placebo twice daily (n=76) Treatment duration: 8 months	To assess the effectiveness of long term treatment with erdosteine in patients with moderate chronic obstructive pulmonary disease (COPD)	After 8 months treatment: • Significantly fewer **exacerbations per patient** in the erdosteine group compared to placebo [0.94 (1.12) versus 1.38 ± 1.39; p<0.01]. • Significantly fewer **hospitalizations per patient** with erdosteine compared to placebo [0.16 (0.57) versus 0.31 (0.74); p<0.05]. Conclusion: Long term treatment with erdosteine in stable COPD patients is associated with fewer exacerbations and hospitalizations which were sustained over an 8-month period.
Clinical evaluation of erdosteine efficacy and tolerability (300 mg capsule) in the treatment of acute, subacute and chronic exacerbated rhinopharyngitis and	To evaluate the efficacy and tolerability of erdosteine versus	At day 7, treatment difference was not significant for the following outcome measures evaluation: • **nasal secretion** (mean difference -0.55 in erdosteine group versus -0.25 in NAC group;

Study type and design (n)	Objective(s)	Primary efficacy endpoint
pharyngolaryngotracheitis. **[Cerqua N. In-house synopsis, 1991]** Phase III, double-blind, randomised, active-controlled, study Male and female with acute, subacute, chronic sinusitis in exacerbation, nasal secretion, retronasal drainage, sinusal pain. n=40 (20 – 72 years, mean age 44.4 years) Two treatment arms (Randomisation ratio 1:1): i) Erdosteine 300mg twice daily (n=20) ii) N-acetylcysteine (NAC) 300mg twice daily (n=20) Treatment duration: 7 days	N-acetylcysteine (NAC) in the treatment of acute, subacute and chronic exacerbated rhinopharyngitis and pharyngo-laryngotracheitis.	p>0.05). • **nasal obstruction** (mean difference -0.85 in erdosteine group versus -0.9 in NAC group; p>0.05) **hyposmia** (mean difference -0.8 in erdosteine group versus -0.9 in NAC group; p>0.05). • **expectoration** (mean difference -0.7 in erdosteine group versus -0.35 in NAC group; p>0.05). • **hyperemia of mucosa** (mean difference -0.9 in erdosteine group versus -0.8 in NAC group; p>0.05). • **oedema of mucosa** (mean difference -1.0 in erdosteine group versus -0.8 in NAC group; p>0.05). • **swallowing pain** (mean difference -1.1 in both groups; p>0.05). • **hoarseness** (mean difference -1.05 in erdosteine group versus -1.15 in NAC group; p>0.05). • **rhinomanometry** (mean difference -0.23 in erdosteine group versus -0.45 in NAC group; p>0.05). Conclusion: Erdosteine was comparable to NAC in improving clinical symptoms with no significant between-treatment difference.

<u>Dispersible tablet</u>

The sponsor had considered the need of a bioequivalence study between erdosteine 300mg hard capsules and dispersible tablets but it was excluded based on the following information:

- A bioequivalence study between erdosteine 300mg hard capsules and powder for oral suspension (sachet) was conducted to confirm the equivalence of these two formulations. In view that erdosteine 300mg powder for oral suspension and dispersible tablets are both aqueous solutions at time of administration, these two formulations are considered equivalent.
- In addition, comparative dissolution data between erdosteine 300mg dispersible tablets, hard capsules and powder for oral suspension at different pHs (pH 1.2, pH 4.5 and pH 6.8) was provided. The results showed rapid dissolution with more than 85% dissolved in 15 minutes and for this reason can be considered similar without further statistical evaluation.

- Based on literature review, excipients used in the dispersible tablet does not affect gastro-intestinal transit and/or absorption of the active ingredient. Additionally, the potential impact of excipients used in hard capsules and dispersible tablet on cellular absorption has also been investigated and ruled out through a comparative permeability test on human intestinal epithelial cells.

2.3 Safety

- The safety profile of erdosteine was generally acceptable with the most commonly reported adverse events (AEs) being gastrointestinal disturbances, most frequently gastralgia and nausea.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 346th meeting on 9th July 2020 has decided to approve the registration of this product with the following indication:

Mucolytic agent for use in adults with acute and chronic respiratory disorders associated with excessive mucus production.