Cost-effectiveness of Cysteamine bitartrate delayed-release (PROCYSBI) for the treatment of patients with nephropathic cystinosis

The NCPE has issued a recommendation regarding the cost-effectiveness of Cysteamine bitartrate delayed-release (PROCYSBI). Following NCPE assessment of the applicant's submission, Cysteamine bitartrate delayed-release (PROCYSBI) is not considered cost-effective for the treatment of patients with nephropathic cystinosis. PROCYSBI is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Horizon Pharma) economic dossier on the cost effectiveness of Cysteamine bitartrate delayed-release (PROCYSBI). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **November 2017**

Summary

Horizon Pharma submitted an economic dossier on the cost-effectiveness of cysteamine bitartrate delayed – release (PROCYSBI) for the treatment of nephropathic cystinosis patients on the 11th July 2017. The product obtained European marketing approval in 2013 and is available as 25mg and 75mg capsules. The recommended daily dose is based on body surface area (BSA) from the RP 103 trial e.g. patients aged 5, 10, 15 and 18 years or older are treated with PROCYSBI 856mg, 1,153mg, 1,449mg and 1,672mg once daily, respectively.

Cystinosis is an autosomal recessive disease caused by a defect in the CTNS gene which encodes for cystinosin, a lysosomal cystine transporter. The defect in cystinosin results in the accumulation and crystallisation of cystine in cells and organs throughout the body. As is the case with many lysosomal storage diseases, initial manifestations appear several months after birth. There are many symptoms and signs however renal involvement remains the main clinical characteristic of the condition.

Cysteamine is an aminothiol that participates within lysosomes in a thiol-disulphide interchange reaction converting cystine into cysteine and cysteine-cysteamine mixed disulphide and both can exit the lysosomes. PROCYSBI is a novel formulation using a beaded, enteric-coated, delayed release form of cysteamine bitartrate, in which microspheronized beads are further encapsulated in a hard gelatine capsule. White blood cell (WBC) cystine is monitored in patients to determine adequacy of dosing and untreated patients with nephropathic cystinosis have elevations of WBC cystine above 2 nmol ½ cystine/mg protein. Cysteamine bitartrate delayed release (DR) preparation (PROCYSBI) is an alternative to the immediate release (IR) preparation (CYSTAGON) which is currently the standard of care for patients with cystinosis. PROCYSBI is an alternative for those patients who are poorly controlled on or cannot tolerate the immediate release preparation.

1. Comparative effectiveness

The clinical evidence for cysteamine bitartrate delayed release preparation (PROCYSBI) presented to the NCPE consisted of nine studies including a head to head trial, five

bioequivalence studies, an open-label extension study and two ongoing, long-term open label trials and all were considered by the NCPE review group.

Study RP103-03 was an open label, randomised controlled, crossover pivotal phase III trial which aimed to demonstrate the non-inferiority of cysteamine bitartrate DR versus IR (Cystagon) for the control of WBC cystine levels. Secondary objectives included an evaluation of the safety and pharmacokinetics of cysteamine bitartrate DR. Forty three patients were randomised, but two patients withdrew from the study therefore 41 patients received treatment with cysteamine bitartrate DR. The mean age of patients in the per-protocol population was 11.9 +/- 4.33 years and 23 were male. There were a number of inclusion criteria including the fact that patients should be receiving a stable dose of cysteamine bitartrate IR defined by the investigators as sufficient to maintain a white blood cell cystine level ≤ 2.0 nmol hemicystine/mg protein.

The primary end-point of the study was white blood cystine levels evaluated on days 5, 6 and 7 of week 6 (period 1) and week 9 (period 2). In the per-protocol population, the mean maximum WBC cystine level was 0.44 ± 0.05 nmol hemicystine/mg protein in patients treated with cysteamine bitartrate IR six hourly and 0.51 ± 0.05 nmol hemicystine/mg protein in patients receiving treatment with cysteamine bitartrate DR twice daily. The reported difference between the two treatments was 0.08 ± 0.03 nmol hemicystine/mg protein (CI 95.8% [0.0107; 0.1464], p<0.0001). The non-inferiority of cysteamine bitartrate DR was demonstrated.

Results from the intention to treat population demonstrated a greater reduction in the maximum WBC cystine level during treatment with cysteamine bitartrate DR preparation (0.53 ± 0.14 nmol hemicystine/mg protein) as compared with the immediate release preparation (0.74 ± 0.14 nmol hemicystine/mg protein) resulting in a difference of -2.1 ± 0.13 nmol hemicystine/mg protein (CI [-0.48; 0.06], p<0.001).

Quality of life (QoL) data was presented and the manufacturer highlighted the fact that the extension study (RP 103-04) showed significant 24 month improvements in three QoL measures as patients switched from the IR preparation to PROCYSBI i.e. social function,

school function and total function. Study RP 103 – 04 was an open label extension trial of study RP103-03 and demonstrated the efficacy of cysteamine bitartrate DR on the maintenance of optimal WBC cystine levels, renal function, somatic growth and impact on quality of life.

A number of pharmacokinetic and bioequivalence studies were presented (RP 103-01, 02, 05, 06 and 09) which demonstrated the bioequivalence of cysteamine bitartrate DR in a number of different scenarios. An assessment of halitosis based on the evaluation of DiMethylSulfide (DMS) in the exhaled air was performed in a subset of RP 103-07 patients. A total of 20 patients were studied and the evaluation of the normalised AUC 0-24 of the DMS showed that it was lower with cysteamine bitartrate DR than with the IR preparation (ratio: 0.74 IC90% [0.52;1.06]) which represented a reduction of 26%. However the NCPE review group noted that this reduction was not statistically significant and that there is no consensus on a threshold DMS concentration that may be deemed clinically relevant. The manufacturer's submission indicates that the delayed release preparation will translate into improved adherence (as compared with the immediate release preparation) however the NCPE review group considers the evidence to support this assumption is not convincing.

2. Safety

The RP 103-03 study provides information in relation to the relative safety of cysteamine bitartrate DR and IR preparations. During the study period 13 patients (31.7%) and 25 patients (58.1%) developed at least one adverse event while receiving the IR and DR preparations, respectively. It is seen that 4.9% of patients treated with cysteamine bitartrate IR preparation developed a moderate (Grade 2) or severe (Grade 3) adverse event as compared with 23.3% of patients treated with the DR preparation.

The most frequent adverse events reported for the DR preparation included gastrointestinal disorders (32.6%), nervous system disorders (14%), metabolism and nutrition disorders (9.3%) and vascular side effects (9.3%). No patient in either arm of the study developed a Grade 4 adverse event. Only one patient withdrew from the study during treatment with the cysteamine bitartrate DR formulation due to the development of cellulitis after elective knee surgery. There were no deaths reported in the RP 103-03 study. The safety data

obtained over the two years of treatment with cysteamine bitartrate DR preparation are in keeping with the findings of the RP 103-03 pivotal study and confirm its safety profile.

3. Cost effectiveness

The cost effectiveness of cysteamine bitartrate DR was assessed using a Markov model, with a one year cycle length. The model time horizon is a lifetime horizon of 100 years. The population in the economic model reflected the therapeutic indication i.e. patients with nephropathic cystinosis who are poorly controlled on cysteamine bitartrate immediate release (IR) or those who are unable to tolerate the IR formulation.

Patients are at risk of end stage renal disease (ESRD), diabetes mellitus (DM) and neuromuscular disorders (NMD) dependent on treatment compliance and control of WBC cystine levels. The Markov model includes 8 health states including (i) no ESRD no DM and no NMD (ii) no ESRD no DM but NMD (iii) no ESRD no NMD but DM and (iv) no ESRD but DM and NMD. The remaining four health states include (v) ESRD no DM and no NMD (vi) ESRD no DM but NMD (vii) ESRD no NMD but DM and (viii) ESRD and DM and NMD. The additional health state was the death state and survival curves were modelled on data reported by Brodin-Sartorius (2012) following either a Weibull or Gompertz distribution. The risk of complications were mainly derived from the Brodin-Sartorius publication but amended by expert opinion. Results in the base case represent the perspective of the Health Service Executive (HSE) and wider societal costs and benefits were not included. A discount rate of 5% was applied in line with current guidelines

The NCPE review group considered that the estimates of median age to complications such as ESRD, diabetes mellitus and neuromuscular disease for the two treatment groups were associated with a significant degree of uncertainty in the model. The median age to death is assumed to be 23 years for the IR preparation whilst the median age to death for the DR preparation is 50 years. As there is no clinical trial data to support this assumption the NCPE review group considered this a major source of uncertainty in the economic model.

Outcomes were expressed as quality adjusted life years i.e. QALYs and life years gained (LYG). The publication by Langman et al. (2014) was used to determine baseline utility in

cystinosis. The individual PedsQL scores were converted to an EQ-5D score using the mapping algorithm developed by Khan et al. (2014). The baseline utility of nephropathic cystinosis in the absence of the three main complications (ESRD, DM and NMD) that are modelled was estimated at 0.95. The disutility of the complications included in the economic model were derived from Dale et al. (2008) for ESRD and DM and Kobelt et al (2006) for NMD. The disutility for ESRD was 0.18 and disutility values for haemodialysis (0.56), peritoneal dialysis (0.35), transplant – first year (0.17) and transplant – subsequent years (0.12) were also determined. The disutility for DM was 0.16 and for NMD was estimated at 0.48.

The model incorporates cost data on drug acquisition, health states, physician visits and costs of clinical complications. The list price for cysteamine bitartrate DR preparation (PROCYSBI) provided in the submission was €468.88 for 60 of the 25mg capsules and €5,861.03 for 250 of the 75mg capsules. The list price for the immediate release preparation (Cystagon) was €76.74 for 100 of the 50mg capsules and €208.27 for 100 of the 150mg capsules. The price per mg of cysteamine bitartrate is over 22 fold greater for the DR preparation (PROCYSBI) as compared with the IR preparation (Cystagon). An estimate of the cost of treating a 10 year old with PROCYSBI for a year is approximately €131,108 (list price, dose of 575mg twice daily). In contrast the annual cost of Cystagon is estimated at €8,570.

The base case analysis of costs and outcomes for cysteamine bitartrate DR versus IR for patients receiving no IR treatment demonstrated an incremental cost effectiveness ratio (ICER) of €539,601/QALY or €492,795/LYG. Corresponding ICERs for patients on cysteamine bitartrate DR versus patients on cysteamine bitartrate IR who are 30% compliant were estimated at €387,768/QALY and €486,994/LYG. A deterministic and probabilistic sensitivity analysis was presented. The parameters that impacted QALYs the most were discount rates, utility values and the dose of cysteamine bitartrate DR. Regardless of the change in parameter values all ICERs exceeded €400,000/QALY.

4. Budget impact

The gross budget impact when cysteamine bitartrate DR is reimbursed is estimated as €701,320 in year one increasing to €1,306,914 in year 5. The cumulative budget impact over the 5 year period was estimated at €5,202,262. The net budget impact associated with the reimbursement of cysteamine bitartrate DR is €583,683 in year one increasing to €1,189,276 in year 5. The cumulative net budget impact over 5 years was estimated at €4,614,076.

5. Conclusion

As compared with cysteamine immediate release PROCYSBI treatment is not associated with significant additional health outcome benefits and cannot be considered a cost-effective alternative to the current standard of care CYSTAGON. In view of this the NCPE does not recommend reimbursement of the cysteamine bitartrate delayed release preparation PROCYSBI at the submitted price.