



Cost-effectiveness of lesinurad (Zurampic®) for the treatment of adult patients with gout

The NCPE has issued a recommendation regarding the cost-effectiveness of Lesinurad (Zurampic®) in combination with a xanthine oxidase inhibitor for the treatment of gout. The NCPE recommends that lesinurad should not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Grunenthal Pharma Ltd) economic dossier on the cost effectiveness of Lesinurad for gout. 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.

Summary

Grunenthal Pharma Ltd submitted an economic dossier (7th June 2018) on the cost-effectiveness of lesinurad (Zurampic®) when used in combination with a xanthine oxidase inhibitor to treat adult patients with gout. Lesinurad is an inhibitor of urate transporter 1 (URAT1) an anion exchanging uptake transporter located in the renal proximal tubule. This results in an increase in the excretion of uric acid. Lesinurad also inhibits organic acid transporter 4, another uric acid transporter at the proximal renal tubule. Marketing authorisation was granted on the 19th February 2016. The recommended dose of lesinurad is 200 mg orally once daily in combination with a xanthine oxidase inhibitor for the treatment of hyperuricaemia in patients with gout who have failed to achieve a target serum uric acid level of less than 360 µmol/l despite an adequate dose of allopurinol or febuxostat.

Gout is a disorder of purine metabolism where clinical manifestations include acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis and gouty nephropathy resulting from the deposition of monosodium urate or uric acid crystals from supersaturated body fluids. The prevalence of gout is thought to range between 0.9% to 2.5% in European countries and increases with age and is higher in men. When urate concentrations exceed 380µmol/l the risk of monosodium urate crystal formation increases. The National prescribing database indicates that 30,256 patients are currently being treated with xanthine oxidase inhibitors where 78% are receiving allopurinol (n = 23,468) and 6,788 patients receiving febuxostat.

1. Comparative effectiveness

The submitted dossier highlights three randomised controlled clinical trials of lesinurad including the CLEAR 1 and CLEAR 2 trials in addition to the CRYSTAL study. Supporting evidence from two open-label extension studies included Study 306 which was an extension of the CLEAR 1 and CLEAR 2 studies and Study 307 an extension of the CRYSTAL study.

The Combining Lesinurad with Allopurinol Standard of Care in inadequate Responders (CLEAR 1) study was a 12 month multicentre, randomised, double-blind, placebo controlled trial of lesinurad (200mg or 400mg) in combination with allopurinol versus placebo plus allopurinol in patients with gout and a serum uric acid level above a target of 6.0 mg/dl (equivalent to 357 $\mu\text{mol/l}$). The study included 603 patients who received ≥ 300 mg/day allopurinol (≥ 200 mg/day in those with moderate renal impairment) who had serum uric acid levels ≥ 6.5 mg/dl (386 $\mu\text{mol/l}$) at screening and ≥ 2 gout flares during the previous year. The primary end-point was the proportion of patients achieving a serum uric acid level of less than 6 mg/dl (< 357 $\mu\text{mol/l}$) at month 6. Secondary end-points included the mean gout flare rate requiring treatment (months 7 – 12) and the proportion of patients with complete resolution of ≥ 1 target tophus (month 12). Safety assessments included adverse drug events and laboratory parameters.

Lesinurad at doses of 200 mg and 400 mg in combination with allopurinol significantly increased the proportion of patients who achieved target levels of serum uric acid (< 357 $\mu\text{mol/l}$) by month 6 as compared with allopurinol monotherapy (54.2%, 59.2% and 27.9% respectively, $P < 0.0001$). There was no significant difference in the rates of gout flares and complete resolution of gouty tophi.

The CLEAR 2 study was a twelve month International randomised, placebo-controlled phase III clinical trial to investigate the efficacy and safety of two lesinurad doses (200 mg and 400 mg daily) in combination with allopurinol versus allopurinol combined with placebo. The study was similar to the CLEAR 1 study and included 610 patients who received ≥ 300 mg/day allopurinol (≥ 200 mg/day in those with moderate renal impairment) who had serum uric acid levels ≥ 6.5 mg/dl (386 $\mu\text{mol/l}$) at screening and ≥ 2 gout flares during the previous year. The primary end-point was the proportion of patients achieving a serum uric acid level of less than 6 mg/dl (< 357 $\mu\text{mol/l}$) at month 6. Secondary end-points included the mean gout flare rate requiring treatment (months 7 – 12) and the proportion of patients with complete resolution of ≥ 1 target tophus (month 12). Safety assessments included adverse drug events and laboratory data.

Lesinurad at 200 mg and 400 mg doses in combination with allopurinol significantly increased the proportion of patients achieving target serum uric acid levels ($< 357 \mu\text{mol/l}$) versus allopurinol + placebo by month 6 (55.4%, 66.5% and 23.3% respectively, $p < 0.0001$ for both lesinurad groups). There was no significant difference between the groups in relation to clinical outcomes i.e. the mean gout flare rate requiring treatment or the complete resolution of one or more target tophi by month 12.

The Combination Treatment Study in Subjects with Subcutaneous Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) was a phase III multicentre, randomised, double-blind, placebo-controlled combination study evaluating the efficacy and safety of lesinurad 200 mg or 400 mg orally in combination with febuxostat 80 mg orally compared with placebo in combination with febuxostat 80 mg. Patients with a serum urate $\geq 8 \text{ mg/dl}$ ($475 \mu\text{mol/l}$) or $\geq 6 \text{ mg/dl}$ ($357 \mu\text{mol/l}$) in patients being treated with urate lowering therapy and ≥ 1 measurable target tophus were given febuxostat 80 mg/day for 3 weeks before randomisation to receive lesinurad (200 mg or 400 mg daily) or placebo in addition to febuxostat. The primary end-point was the proportion of patients achieving a serum uric acid level $< 5 \text{ mg/dl}$ ($297 \mu\text{mol/l}$) by month 6. Secondary end-points included the proportion of patients with complete resolution of ≥ 1 target tophus by months 12. Other end-points included the percentage change in total target tophi area. Safety assessments included adverse drug reactions and laboratory parameters.

Significantly more patients achieved the serum uric acid target of $297 \mu\text{mol/l}$ by month 6 with the addition of lesinurad 400 mg/day (76.1%; $P < 0.0001$) but not with lesinurad 200 mg/day (56.6%) to febuxostat therapy as compared with febuxostat alone (46.8%). The rate of gouty flares requiring treatment did not differ significantly between febuxostat + lesinurad 200 mg/day versus febuxostat alone. The number of patients with complete tophus resolution was not different between the treatment groups.

2. Safety

The main clinical safety information was derived from the pivotal trials. In the CLEAR 1 study lesinurad was reasonably well tolerated. Adverse events resulting in treatment

discontinuation were higher in the lesinurad groups (8% in the lesinurad 200mg/day + allopurinol group and 7% in the lesinurad 400mg/day + allopurinol group) as compared with 4% for allopurinol monotherapy. Corresponding figures from the CRYSTAL 2 study were 5.3%, 3.4% and 9.5% respectively. Common adverse events included upper respiratory tract infections, increased creatine kinase (CK), sinusitis and raised creatinine.

Renal related adverse events, including elevation of the serum creatinine above 1.5 times the baseline levels were more noticeable with the higher 400mg/day dose of lesinurad in the pivotal trials. Lesinurad treatment should be discontinued in patients with a creatinine clearance persistently below 30 ml/min and it is contraindicated in patients with end-stage renal disease, kidney transplant recipients and patients undergoing dialysis.

The NCPE review group concluded that the main clinical safety issue relates to cardiovascular risk with lesinurad. It is envisaged that a post authorisation safety study (PASS) will provide additional data to characterise the cardiovascular safety of lesinurad in combination with a xanthine oxidase inhibitor in patients 18 years of age or older.

3. Cost effectiveness

The intervention under assessment is the combination of lesinurad 200 mg orally + allopurinol once daily versus daily allopurinol monotherapy or febuxostat monotherapy. The base-case analysis included a stopping rule where patients who do not reach a serum uric acid target of less than 360 $\mu\text{mol/l}$ with lesinurad + allopurinol at 6 months are assumed to discontinue lesinurad but remain on monotherapy with either allopurinol or febuxostat. The cost effectiveness of lesinurad in combination with allopurinol was assessed using a Markov cohort model with a cycle length of 6 months and a 50 year time horizon.

Data from the 12 month randomized CLEAR studies were used to inform second line efficacy of lesinurad. Flares on treatment beyond the first year were extrapolated from the month 12 flare rates. Separate parameters were estimated for each combination of disease state and serum uric acid category, the parameters that control the changes in flare rates per month for uric acid levels < 8 mg/dl (475.84 $\mu\text{mol/l}$) were estimated from post hoc analysis

of the CLEAR extension trial (Study 306) while parameters controlling flare rates per month for uric acid levels ≥ 8 mg/dl ($475.84 \mu\text{mol/l}$) were estimated from a post hoc analysis of the LASSO trial. Gout related mortality risk from epidemiology studies were used to support extrapolation in the long term. Health states in the model are stratified by tophus status (non-tophaceous gout, tophaceous gout), serum uric acid category after treatment (<5 mg/dl, 5 to <6 mg/dl, 6 to <8 mg/dl, 8 to 10 mg/dl, ≥ 10 mg/dl) and treatment status (second-line uric acid lowering therapy (ULT), first-line ULT, no ULT). Patients enter the model on initiation of second line uric acid lowering therapy having failed first line treatment with a physician led clinically appropriate dose of allopurinol, defined as a serum uric acid level ≥ 6 mg/dl ($360 \mu\text{mol/l}$). Reversion to first line uric acid lowering therapy is modelled to represent a treatment path for patients who are intolerant and/or non-responsive to second line treatment. Results in the base case represent the perspective of the Health Service Executive (HSE). Health outcomes in the economic evaluation were expressed as quality adjusted life years i.e. QALYs. A regression analysis of the SF-6D scores in CLEAR 1 and CLEAR 2 was performed to provide trial based utilities for both flares and tophi. The model incorporates cost data on gouty flares requiring treatment, drug acquisition costs, health state and adverse event costs. The price to wholesaler cost for lesinurad was €25.20 resulting in a total reimbursement cost of €30.89 per 30 tablet pack. A summary of costs by health states including non - tophaceous gout and tophaceous gout with 0, 1 – 2 flares, 3 – 5 flares and ≥ 6 flares was also provided. Similarly, values for QALY gains by health state were also provided. A discount rate of 5% was applied in line with current guidelines.

An incremental analysis of costs and QALYs was presented and the base case analysis indicates that the cost/QALY for lesinurad + allopurinol versus allopurinol monotherapy is €24,381/QALY and the cost-effectiveness of lesinurad + allopurinol versus febuxostat monotherapy is €19,181/QALY. Probabilistic analysis indicates slightly higher ICERs just exceeding €30,000/QALY. The probability of lesinurad + allopurinol being cost-effective at the €45,000/QALY threshold as compared with allopurinol monotherapy and febuxostat monotherapy exceeded 85% and 65% respectively.

4. Budget impact

The 5 year gross budget impact increases from €197,989 in year 1 to €1,661,935 in year 5 resulting in a cumulative 5 year gross budget impact of €4,195,329. The net 5 year budget impact was estimated at € 439,585. The NCPE review group considered these figures an underestimate as the number of patients that are identified as being treated with xanthine oxidase inhibitors is higher than presented in this submission and the predicted market uptake was too low.

5. Conclusion

The NCPE review group consider the manufacturer's cost-effectiveness estimates to be too low and highlight that the clinical trials did not show any significant difference in quality of life with lesinurad in combination with a xanthine oxidase inhibitor as compared with xanthine oxidase monotherapy and there is no evidence to support the modelling assumption that lowering serum uric acid extends life. We also consider the 5 year budget impact an underestimate.

Therefore we do not believe that the manufacturer has demonstrated lesinurad to be cost-effective and has underestimated the budget impact. In addition, there are ongoing concerns in relation to cardiovascular adverse events. Furthermore, the clinical trial data does not demonstrate any benefit of lesinurad plus a xanthine oxidase inhibitor over current second line therapy i.e. febuxostat monotherapy. The NCPE recommends that lesinurad not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.