Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

Evidence review for Surrey & North West Sussex Area Prescribing Committee (APC)

Medicine details	
Name, brand name	Acetazolamide
Manufacturer	Manufacturer(s)
Proposed indication	Idiopathic Intracranial Hypertension (IIH)
Requested by	Neurology (Graham Warner / Athinodoros Valavanis)

SUMMARY

Clinical Effectiveness

Carbonic anhydrase inhibitors are believed to reduce the rate of cerebrospinal fluid (CSF) production and have been associated with modestly improved outcomes in patients with IIH.

In a randomised trial of 165 patients with IHD and mild visual loss (1) Idiopathic Intracranial Hypertension treatment trial [IIHTT], treatment with acetazolamide was associated with modest improvements in a perimetric measurement of global visual field loss, along with improvements in papilledema grade CSF pressure and vision-related quality of life at 6 months, when added to a low sodium weight reduction diet in patients with IIH and mild visual loss(2). More patients in the placebo group had poor visual outcome compared with those in the acetazolamide treatment group (one versus six).

Other observational evidence supports the use of acetazolamide.

Lowered CSF pressure with acetazolamide has been documented in IIH patients, who underwent continuous intracranial pressure (ICP) recordings. Case studies also suggest that in patients who can tolerate it, acetazolamide is successful in managing symptoms and stabilising vision in 47-67% of patients. In addition, in a long term follow up study of 54 patients, the average treatment duration of acetazolamide was 14 months. While recurrent episodes of IIH occurred in 38% over a mean 6.2 years of follow up, no recurrences occurred in the setting of ongoing acetazolamide treatment.

Safety

Medication side effects of acetazolamide: Common: Paraesthesia, nausea, fatigue, headache, taste disturbance, vomiting, diarrhoea, dizziness, ataxia, depression, excitement, flushing, irritability, loss of appetite, increased frequency of urination, reduced libido, thirst. Uncommon: tinnitus, rash, bone marrow suppression, confusion, drowsiness, electrolyte disturbance, fever, glycosuria, haematuria, melena, metabolic disturbance, kidney stones, kidney failure. These are usually dose related. While many patients with IIH experienced side effects of acetazolamide, quality-of-life measures were still higher in patients who received acetazolamide. In patients with IIH, it has been found that monitoring of electrolytes during acetazolamide treatment is not necessary if acetazolamide is the only diuretic used.
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk of Acetazolamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation emerge.

Patient factors

No commissioning factors to consider. PbR drug. Enabling acetazolamide to become a blue drug, initiated and stabilised by the Consultant Neurologist, with GP continuing prescribing will improve the patient journey and hopefully patient outcomes.

Renal function to be monitored, (extra doses to be considered in dialysis patients) hypokalaemia, hyponatraemia is a risk. History of sulphonamide hypersensitivity (e.g. sulfamethoxazole/trimethoprim) is a contra-indication
Cautions: Diabetes Mellitus, impaired alveolar ventilation or pulmonary obstruction. Renal stones. Long term use, elderly, liver dysfunction.
Acetazolamide should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.
DDI's – High dose aspirin increases the risk of toxic reaction, causes problems with Lithium, Increases risk of overheating and dehydration if taken with Zonisamide. Makes Methotrexate and Methenamide not work as well
MHRA – There are 3 MHRA safety information alerts issued under the heading relating to Acetazolamide. The main safety concern is that the drug is known to cause birth defects. Therefore not to be used in pregnancy women.

Cost implications

Minimal – drug is not expensive
There is no right dose for patient with IIH. The most commonly used starting dose is 250mg-500mg twice daily and the dose can be increased slowly if appropriate. The max dose recommended varies from 2g – 4g daily.
One study showed 48% of their patients stopped the drug at a daily dose of 1.5g due to side effects.
One 250mg tablet is 5p therefore 10p per day, 28p per month for a dose of 250mg BD PER PATIENT
The benefits outweigh the cost implications because the vision of even one young adolescent is worth saving by use of the drug.

Relevant guidance / reviews

40088.embase.pdf

The HDAS Export report above shows additional references supporting the use
Of Acetazolamide in IIH

Likely place in therapy relative to current treatments

Suggestion that this medicine should be Blue, with initiation and stabilisation by Consultant.
No concerns that prescribing will take place out of recommended guidelines
Topiramate and Bendroflumethiazide are standard medicines, which are also used for this indication and are unlicensed for this indication. The overall management strategy can be relatively easily extended since the supporting evidence is similar (lots of studies, low profit meds, common usage). Similarly for short sharp courses of corticosteroids. Low profit medications used in this condition mean that pharmaceutical companies are unlikely to apply for licensing.

Recommendation to APC

Blue status recommendation with initiation and stabilisation by Consultant.

Medicine details

Name and brand name	Acetazolamide
Licensed indication, formulation and usual dosage	Available as generic SR capsules 250mg and standard release tablets 250mg. The preparation recommended for this indication is the standard release, for the majority of patients. As the condition is often seen in adolescents, slow release may enhance compliance and so should be included in the application. THE USE OF THIS DRUG FOR THIS INDICATION IS UNLICENSED. Many medicines used in neurology are also unlicensed for their indication, particularly migraine.
Summary of mechanism of	Acetazolamide is an enzyme inhibitor which acts specifically on carbonic anhydrase. Acetazolamide is a sulphonamide derivative.

action, and relevant pharmacokinetics	Absorption: - Acetazolamide is fairly rapidly absorbed from the GI tract with peak plasma concentrations occurring 2 hours after administration by mouth Distribution:- It has been estimated to have a plasma half-life of about 4 hours. It is tightly bound to carbonic anhydrase and accumulates in tissues containing this enzyme, particularly red blood cells and the renal cortex. It is also bound to proteins. Elimination – It is excreted unchanged in the urine; renal clearance being enhanced in alkaline urine. Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and / or paraesthesia.
Important drug interactions	Sulphonamides may potentiate the effects of folic acid antagonists, hypoglycaemics and oral anticoagulants. Concurrent administration of acetazolamide and aspirin may result in severe acidosis and increase CNS toxicity. Adjustment of dose may be required when acetazolamide is given with cardiac glycosides or hypertensive agents. Because of possible additive effects, concomitant use with other carbonic anhydrase inhibitors is not advisable. By increasing the Ph of renal tubular urine, acetazolamide reduces the urinary excretion of amphetamine and quinidine and so may enhance the magnitude and the duration of effect of amphetamines and enhance the effect of quinidine. Ciclosporin- Acetazolamide may elevate ciclosporin levels Methenamine- Acetazolamide increases lithium excretion and blood lithium levels maybe decreased Sodium Bicarbonate – Acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculus formation.
Monitoring requirements	When prescribed long term, special precautions are advisable The patient should be counselled to report any unusual skin rash. Periodic blood cell counts, and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulphonamides. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of acetazolamide therapy. In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, acetazolamide may aggravate acidosis and should be used with caution. In patients with a past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP). In case of AGEP diagnosis, acetazolamide should be discontinued, and any subsequent administration of acetazolamide contraindicated.
Prescribing considerations	Likely BLUE traffic light status Colour classification guidelines
Other considerations	N/A

Potential patient group (if appropriate to include)	
Brief description of disease	Idiopathic intracranial hypertension (IIH) happens when high pressure/volume of the CSF (cerebrospinal fluid) causes symptoms like vision changes and headaches
Potential patient numbers per 100,000	1 per 100.000, in obese young females can be up to 20 per 100.000 Orpha.net quotes 1 – 50 /10,000 (or 10 to 500/100,000)
Outcomes required	1. avoidance of visual loss whilst pt loses wt. 2. reduction of headache Sx (NB many pts continue to get headaches even once normalised ICP is achieved with migrainous features that need more basis headache care potentially within competencies that do not need specialist

	knowledge)

Summary of current treatment pathway

Advise about weight management to all with BMI > 30kg/m2
If no immediate, treat for vision consider Acetazolamide.
The only strong evidence for "cure" is weight loss. We could consider expanding this to bariatric surgery. The aim of the drug is to buy time for weight loss, and therefore prevention of blindness. Weight loss remains the ultimate goal.
We can't advise a specific weight loss goal but weight loss will have an impact on symptom control as well as intracranial pressure (measure by lumbar puncture). These parameters will define effectiveness of treatment

Idiopathic intracranial hypertension: consensus guidelines on management
Mollan SP, et al. J Neurol Neurosurg Psychiatry 2018;89:1088–1100. doi:10.1136/jnnp-2017-317440

Evidence review

40088.investop.pdf 40088.jama.pdf

Recommendations from national / regional decision-making groups	Include conclusions or recommendations from NICE, SMC, AWMSG, MTRAC etc None found
Stakeholder views	Views of 2 Consultant neurologists (RSCH) have been sought and they are very keen to progress this application forward (see above for names)
CCG priorities	Does this treatment fit with existing national, regional or local priorities, policies or activity*?* None identified

Health economic considerations

Cost per year per patient

Include annual cost per patient, and population cost per 100,000 people

Worst case scenario for spend on above information based on DT price is between £77k and £706k over the entire ICS per annum.

	Tabs @ £0.06 each	SR Caps @ £0.55 each
Per patient	£350.40	£3212
Per 100,000	£7,008	£64,240
Per place (max 300k)	£21,024	£192,720
ICS wide (1.1mil)	£77,088	£706,640

Alternative treatments cost per patient per year

Include comparable costs of alternative treatments at patient and per 100,000 population if relevant

Topiramate - @400mg daily (IIHUK) = £469.28/patient (£9,385/100,000)

Other financial considerations (if relevant)

Include additional costs such as monitoring costs, and any potential off-set costs

Health economic data (if available)

Include information from relevant health economic analysis, indicate the level of robustness of the analysis

References

1. Wall et al Visual Field Outcomes for the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), *IOVS, March 2016 Vol 57, No 3, Page 806*
2. Wall; Effects of Acetazolamide on Visual Function in patients with Idiopathic Intracranial Hypertension

and Mild Visual Loss, *JAMA 2014, April 23; 311(16) 1641-1651*

Prepared by:

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Declaration of Interest:

None

Date: XXXX

Reviewed by:

Name, Designation, Organisation

Declaration of Interest:

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Date: XXXX