NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Angiotensin II for treating vasopressor-resistant hypotension caused by distributive shock

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of angiotensin II within its marketing authorisation for the treatment of hypotension in adults with septic or other distributive shock who remain hypotensive following catecholamines and other vasopressor therapies.

Background

Hypotension occurs in people in whom there are abnormalities in the autonomic control of cardiovascular function. There are varied causes of hypotension, one of which is acute shock. Shock is defined as a life-threatening reduction of blood flow to the tissues and vital organs[1]. It may be caused by sepsis (bacterial or fungal), anaphylaxis, blood loss (haemorrhage), cardiac dysfunctions (such as myocardial infarction, arrhythmia) or spinal trauma.

Distributive (also known a circulatory) shock is the most common type of shock with about 90% of cases being septic shock. Symptoms of distributive shock include low blood pressure, rapid heartbeat, reduced blood flow to vital organs, confusion and loss of consciousness[2]. Septic shock has been reported to be associated with high risk of mortality despite treatment[3].

There is limited evidence on the incidence estimates for hypotension due to distributive or septic shock from community settings[4] because people with shock are typically treated in intensive care units (ICUs). Epidemiologic data on distributive shock in ICUs are scant but data for septic shock are a reasonable substitute. A recent review of 189 adult intensive care units in England in 2015 found that of a total of 148,502 admissions, 42,688 (28.7%) were admitted with septic shock[5].

The aim of treatment is to restore normal blood pressure (mean arterial pressure of greater than 65 mmHg) and adequate blood supply to vital organs. Management of distributive shock involves correcting the triggering cause and restoring adequate organ perfusion with intravenous fluids, and vasopressor drugs that act on the vascular system to increase blood pressure[6]. The vasopressor choice and additional medications will vary depending on the suspected underlying cause of distributive shock[2]. Severe shock is usually treated with catecholamine vasopressor drugs (e.g. noradrenaline, adrenaline) first line, and vasopressin (a non-catecholamine vasopressor) second line for those who have an insufficient response to

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catecholamines. Shock that does not respond to treatment with these drugs is referred to as resistant (or refractory).

The technology

Angiotensin II (Giapreza, La Jolla Pharmaceutical Company) is synthetic human angiotensin II (a naturally occurring hormone that regulates blood pressure). Angiotensin II is a vasopressor agent that is administered by intravenous infusion via a central venous line or if not available, a peripheral IV may be used.

Angiotensin II does not currently have a marketing authorisation in the UK. It has been studied in a randomized, placebo-controlled trial in adults with septic or other distributive shock who remained hypotensive despite fluid and vasopressor therapy.

Intervention(s)	Angiotensin II (in addition to catecholamines or other non-catecholamine vasopressor therapies)
Population(s)	Adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies
Comparators	Established clinical management without angiotensin II
Outcomes	The outcome measures to be considered include: • Change in mean arterial pressure • Change in total organ function • Change in heart rate • Change in catecholamine dosing • Admission to and duration of critical care (disease progression) • mortality adverse effects of treatment • health-related quality of life.

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Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: Orthostatic hypotension due to autonomic dysfunction: midodrine (2015) NICE evidence summary 61 Postural hypotension in adults: fludrocortisone (2013) NICE evidence summary of unlicensed or off-label medicines 20
Related National Policy	NHS England (2018) Highly specialised services 2017 NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' The NHS Long Term Plan, 2019. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 3, and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is the population defined appropriately?

How is refractory/resistant shock defined in clinical practice?

The company's pivotal trial assessed the effect of angiotensin II as an adjunct to background vasopressors in adults with septic or other distributive shock

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who remain hypotensive despite catecholamines and other available vasopressor therapies:

Is the population defined appropriately?

How is established clinical management for shock not responding to catecholamines and other vasopressor therapies defined?

Will angiotensin II be used together with catecholamines and/or other non-catecholamine vasopressor therapies?

Where does angiotensin II fit in the treatment pathway?

Have all relevant comparators for angiotensin II been included in the scope?

Are the outcomes listed appropriate? Should other outcomes be added?

Are there any subgroups of people in whom angiotensin II is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which angiotensin II will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider angiotensin II to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?

Do you consider that the use of angiotensin II can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

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Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Gaieski DF & Mikkelsen ME. Definition, classification, etiology, and pathophysiology of shock in adults. Available from https://www.uptodate.com/contents/definition-classification-etiology-and-pathophysiology-of-shock-in-adults. Accessed April 2019

2 Smith N and Silberman M. Shock, Distributive. In: StatPearls. Treasure Island (FL): StatPearls Publishing. Available from https://www.ncbi.nlm.nih.gov/books/NBK531492. Accessed March 2019

3 Havel C, Arrich J, Losert H, Gamper G, Müllner M, Herkner H. (2011) Vasopressors for hypotensive shock. Cochrane Database of Systematic Reviews. 2011(5).

4 https://www.nice.org.uk/guidance/ng51/evidence/full-guideline-pdf-2551523297

5 Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database (2017) British Journal of Anaethesia 119(4): 626-636.

6 Jentzer JC, Vallabhajosyula S, Khanna AK et al. (2018) Management of Refractory Vasodilatory Shock. Chest 154(2): 416-426.

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