SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Axumin 3,200 MBq/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Axumin 3,200 MBq/mL solution for injection

Each mL of solution contains 3,200 MBq of fluciclovine (^{18}F) at the date and time of calibration (ToC).

The activity per vial ranges from 3,200 MBq to 32,000 MBq at the date and ToC.

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Excipients with known effect
Each mL of solution contains 7.7 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Axumin is indicated for positron emission tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence based on elevated blood prostate specific antigen (PSA) levels after primary curative treatment.

For the limitations in the interpretation of a positive scan, see section 4.4 and 5.1.

4.2 Posology and method of administration

A PET scan with fluciclovine (^{18}F) should be administered by appropriately qualified healthcare professionals.

Images should only be interpreted by readers trained in the interpretation of PET images with fluciclovine (^{18}F).

Posology

The recommended activity for an adult is 370 MBq fluciclovine (^{18}F).

Special populations

Elderly
No dose adjustment required.

Renal and hepatic impairment
Axumin has not been studied in patients with renal or hepatic impairment.
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population
There is no relevant use of fluciclovine (^{18}F) in the paediatric population.

Method of administration

Axumin is for intravenous use.

The activity of fluciclovine (^{18}F) has to be measured with an activimeter immediately prior to injection.

Axumin should be administered as a bolus intravenous injection. The recommended maximum volume of injection of undiluted Axumin is 5 mL. Axumin may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection by a factor of 8. The injection should be followed by an intravenous flush of sterile sodium chloride 9 mg/ml (0.9%) solution for injection to ensure full delivery of the dose.

Axumin is for multidose use.

For instructions on dilution of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition
The patient should be positioned supine with arms above the head. A computed tomography (CT) scan should be obtained for attenuation correction and anatomic correlation. PET scanning should begin from 3-5 minutes (target 4 minutes) after completion of the injection; an acquisition time of 3 minutes per bed position is recommended. Increasing the duration of acquisition over the pelvis may increase the sensitivity of detection of disease. It is recommended that image acquisition should start from mid-thigh and proceed to the base of the skull. Typical total scan time is between 20-30 minutes.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

The PSA value may affect the diagnostic performance of fluciclovine (^{18}F) PET (see section 5.1, Pharmacodynamic properties).

Renal impairment

Careful consideration of the benefit/risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population

For information on use in the paediatric population, see section 4.2.

Patient preparation

It should be recommended to the patient that they do not undertake any significant exercise for at least a day before the fluciclovine (^{18}F) scan.

Prior to administration of fluciclovine (^{18}F), patients should not eat or drink for at least 4 hours (other than small amounts of water for taking medicinal products). In order to mitigate the quantity and intensity of early excretion into the bladder, which may mask or mimic local prostate cancer recurrence, patients should be informed that they may void at the latest 60 minutes before injection of fluciclovine (^{18}F), and should then refrain from voiding until after the scan has been completed.

Interpretation of fluciclovine (18F) images and limitations of use

Fluciclovine (^{18}F) images should be interpreted by appropriately trained personnel.

PET images with fluciclovine (^{18}F) should be interpreted visually. Suspicion of cancer in sites typical for prostate cancer recurrence is based on fluciclovine (^{18}F) uptake in comparison with tissue background. For small lesions (<1 cm diameter) focal uptake greater than blood pool should be considered suspicious for cancer. For larger lesions, uptake equal to or greater than bone marrow is considered suspicious for cancer.

The impact of quantitative/semiquantitative measurement of fluciclovine (^{18}F) uptake as an aid to image interpretation has not been assessed.

Image interpretation errors can occur with PET with fluciclovine (^{18}F) (see section 5.1).

Fluciclovine (^{18}F) uptake is not specific for prostate cancer and may occur with other types of cancer, prostatitis and benign prostatic hyperplasia. False-positive cases have been also described in association with an inflammatory response after cryotherapy and radiation artefacts in patients previously treated with radiotherapy. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, should be considered where appropriate.

The use of either intravenous iodinated CT contrast or oral contrast media is not required to interpret fluciclovine (^{18}F) PET images.

The detection of prostate cancer recurrence in prostate/prostate bed, regional lymph nodes, bone, soft tissue and non-regional lymph nodes by fluciclovine (^{18}F) PET has been reported.

Diagnostic performance of fluciclovine (^{18}F) to detect recurrences has not been investigated in patients with a suspected recurrence based on elevated blood PSA levels after primary radical treatment with a recent positive whole-body bone scintigraphy.

After the procedure

The patient should be encouraged to drink sufficient amounts and void as often as possible during the first hours after the scan in order to reduce radiation exposure of the bladder.

Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Specific warnings

This medicinal product contains up to 39 mg sodium in each injected dose, equivalent to 2% of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The impact of anti-mitotic agents and colony stimulating factors on uptake of fluciclovine in patients with prostate cancer has not been studied.

4.6 Fertility, pregnancy and lactation

Fluciclovine (^{18}F) is not indicated for use in women.

Fertility

No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

Axumin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 8.2 mSv when the maximal recommended activity of 370 MBq is administered these adverse reactions are expected to occur with a low probability.

Tabulated list of adverse reactions

Adverse reactions were reported commonly (≥ 1/100 to < 1/10) during clinical studies.
They are listed below by MedDRA body system organ class.

MedDRA system organ class	**Adverse reactions**
Nervous system disorders	Dysgeusia
Respiratory thoracic and mediastinal disorders	Parosmia
General disorders and administration site conditions	Injection site reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of administration of a radiation overdose with fluciclovine (^{18}F) the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis, frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX12.

Mechanism of action

Fluciclovine (^{18}F) is a synthetic amino acid which is transported across mammalian cell membranes by amino acid transporters such as LAT-1 and ASCT2. The activities of LAT-1 and ASCT2 are known to be upregulated in prostate cancer, providing a mechanism for the enhanced accumulation of fluciclovine (^{18}F) in prostate cancer.

A quantitative correlation between fluciclovine uptake and enhanced fluciclovine influx into cells was not assessed *in vivo* in healthy volunteers or prostate cancer patients.

Pharmacodynamic effects

At the chemical concentrations used for diagnostic examinations, fluciclovine (^{18}F) does not appear to have any pharmacodynamic activity.

Clinical efficacy and safety

The pivotal efficacy data derives from 115 patients recruited into the BED-001 study at Emory University. Patients were adult and elderly men presenting with suspected recurrence, based on elevated blood PSA levels after primary curative treatment of localised prostate cancer and with negative bone scintigraphy. Patients with non-surgical therapy were treated at least 2 years before. Fluciclovine (^{18}F) PET-CT was restricted to the abdomino-pelvic region.

Histopathology standard of truth data was available for 99 of the 115 subjects. Histological assessment of extraprostatic sites (either regional lymph nodes or distant sites) was only conducted for sites with positive image findings.
The diagnostic performance of fluciclovine (^{18}F) PET-CT for the detection of recurrence overall (at any location), and in 3 different locations (prostate/bed, pelvic lymph nodes, and distant metastases) is shown in Table 1. Distant metastases involved distal lymph nodes, soft tissue and bone.

Table 1. Patient and region based diagnostic performance of fluciclovine ^{18}F PET vs histopathology

	Patient based	Location		
		Prostate & prostate bed	Pelvic lymph nodes	Extraprostatic (pelvic and distal recurrence)
N	105	97	24	29
True positive n (%)	73 (69.5)	57 (58.8)	23 (95.8)	27 (93.1)
False positive n (%)	19 (18.1)	27 (27.8)	1 (4.2)	2 (6.9)

True negative n (%)	12 (11.4)	12 (12.4)	0 (0.0)	0 (0.0)
False negative n (%)	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Sensitivity [95% CI]	98.6% (73/74) [92.7 - 100%]	98.3% (57/58) [90.8 - 100%]	100% (23/23) [85.2 - 100%]	100% (27/27) [87.2 - 100%]
Specificity [95% CI]	38.7% (12/31) [21.8 - 57.8%]	30.8% (12/39) [17.0 - 47.6%]		
Positive likelihood ratio [95% CI]	1.61 [1.22 - 2.13]	1.42 [1.15 - 1.75]		
Negative likelihood ratio [95% CI]	0.03 [0 - 0.26]	0.06 [0.01 - 0.41]		

Using the findings of other relevant imaging modalities and clinical follow-up as reference standard in the recruited population, patient-based sensitivity and specificity of fluciclovine (^{18}F) PET-CT for detection of prostate/prostate bed recurrences were 94.7% (89/94) (95%CI: 88.0-98.3%) and 54.8% (17/31) (95%CI:36-72.7%), respectively. For detection of extraprostatic recurrences (regional lymph node and/or distal metastases) sensitivity was 84.2% (32/38) (95%CI: 68.7-94%) and specificity was 89.7% (78/87) (95%CI: 81.3-95.2%), respectively.

The patient-based diagnostic performance of fluciclovine (^{18}F) PET-CT by blood PSA level is shown in Table 2.

Table 2. Effect of blood PSA level on the patient-based diagnostic performance of fluciclovine (^{18}F) PET-CT at BED-001 Emory

	PSA (ng/mL)			
	≤1.05	>1.05 - ≤3.98	>3.98 - ≤8.90	>8.90
No. subjects in analysis	16	31	25	27
True positive (%)	3 (18.8)	23 (74.2)	20 (80)	23 (85.2)
False positive (%)	4 (25)	5 (16.1)	4 (16)	4 (14.8)
True negative (%)	8 (50)	3 (9.7)	1 (4)	
False negative (%)	1 (6.3)	0 (0)	0 (0)	
Sensitivity [95% CI]	75% (3/4) [19.4 - 99.4%]	100% (23/23) [85.2 - 100%]	100% (20/20) [83.2 – 100%]	100% (23/23) [85.2 – 100%]
Specificity [95% CI]	66.7% (8/12) [34.9 - 90.1%]	37.5% (3/8) [8.5 - 75.5%]	20% (1/5) [0.5 - 71.6%]	

An additional study BED002 conducted a blinded read of fluciclovine (^{18}F) PET-CT images from the Emory subset data in BED-001 study by 3 readers. Blinded reads were compared with the histopathological standard of truth. The patient-based

sensitivity of fluciclovine (^{18}F) was higher than 88.6% for all three readers while specificity ranged from 17.2-53.6%.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Axumin in one or more subsets of the paediatric population in diagnosis of amino acid metabolism in solid tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

Fluciclovine (^{18}F) distributes immediately following administration to the liver (14% of administered activity), pancreas (3%), lung (7%), red bone marrow (12%) and heart wall (4%).
Fluciclovine is not incorporated into proteins. Fluciclovine is not metabolised *in vivo*.

Organ uptake

Fluciclovine (^{18}F) accumulates in prostate cancer and other types of cancer but also in normal tissues and some other prostate pathologies (such as benign prostatic hyperplasia, chronic prostatitis, high grade prostatic intraepithelial hyperplasia). In addition, fluciclovine uptake may be increased by an inflammatory reaction to recent radiotherapy or cryotherapy.

Fluciclovine (^{18}F) is preferentially taken up into prostate cancer cells compared with surrounding normal tissues. Uptake by tumours is rapid, with the highest tumour-to-normal tissue contrast between 4 and 10 minutes after injection and continuing for around 30 minutes, with a 61% reduction in mean tumour uptake at 90 minutes after injection.

Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Activity in the brain is low. With increasing time post injection, distributed uptake is apparent and is mostly associated with skeletal muscle. Washout of ^{18}F activity from the blood is such that about half of the maximum ^{18}F concentration in blood is reached by about 1 hour after administration.

Elimination

The major route of elimination is via the renal pathway. Urinary excretion is slow, reaching approximately 3% of administered radioactivity within 4 hours and 5% within 24 hours.

Half-life

The effective half-life of fluciclovine (^{18}F) equates to the radioactive half-life of fluorine (^{18}F), which is approximately 110 minutes.

Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment have not been characterised.

In *in vitro* studies, fluciclovine (^{18}F) was not taken up by common drug transporters indicating a negligible potential for medicinal product interactions.

5.3 Preclinical safety data

Toxicological studies with rats and dogs have demonstrated that with a single intravenous injection no deaths were observed. Toxicity with repeated administration of up to 1000 mcg/kg/day over 14 days in rats and dogs was not observed. This medicinal product is not intended for regular or continuous administration. Long-term carcinogenicity studies have not been carried out.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate

Concentrated hydrochloric acid

Sodium hydroxide

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in sections 6.6 and 12.

6.3 Shelf life

Axumin 3,200 MBq/mL solution for injection

10 hours from the time of calibration (ToC)

In-use

Chemical and physical in-use stability has been demonstrated for Axumin 3,200 MBq/mL for 10 hours.

From a microbiological point of view, unless the method of opening/ dose withdrawal/dilution precludes the risk of microbiological contamination, the medicinal product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

Axumin is supplied in a 10 mL or 15 mL type 1 glass vial sealed with a fluoro-coated chlorobutyl, chlorobutyl or bromobutyl rubber closure and aluminium overseal.

Axumin 3,200 MBq/mL solution for injection

One vial contains 1 to 10 mL of solution, corresponding to 3,200 to 32,000 MBq at calibration time.

Not all pack sizes may be marketed.

As a result of the manufacturing process some vials are distributed with punctured rubber stoppers.

6.6 Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instructions on dilution of the medicinal product before administration, see section 12.

If at any time in the preparation of this medicinal product the integrity of the vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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