Public Assessment Report

Fluorescein Sodium 100 mg/ml, Solution for Injection

(fluorescein sodium)

PL 41349/0001

Viken Pharma Limited
LAY SUMMARY
Fluorescein Sodium 100 mg/ml, Solution for Injection
(fluorescein sodium)

This is a summary of the Public Assessment Report (PAR) for Fluorescein Sodium 100 mg/ml, Solution for Injection (PL 41349/0001). It explains how Fluorescein Sodium 100 mg/ml, Solution for Injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Fluorescein Sodium 100 mg/ml, Solution for Injection.

For practical information about using Fluorescein Sodium 100 mg/ml, Solution for Injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Fluorescein Sodium 100 mg/ml, Solution for Injection and what is it used for?
Fluorescein Sodium 100 mg/ml, Solution for Injection is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Fluorescein Sodium 100 mg/ml, Solution for Injection is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Fluorescein Sodium 100 mg/ml, Solution for Injection is a diagnostic agent used in a hospital-based procedure on the eye called fluorescein angiography of the ocular fundus (part of the eye).

How is Fluorescein Sodium 100 mg/ml, Solution for Injection used?
Fluorescein Sodium 100 mg/ml, Solution for Injection is only administered by a doctor into the antecubital vein (the antecubital vein is situated in the arm) usually through a cannula.

The exact dose, to be determined by a doctor, is up to a maximum dose of Fluorescein sodium 500 mg (equivalent to one 5 ml ampoule) administered by intravenous injection.

Fluorescein Sodium 100 mg/ml, Solution for Injection is not recommended for use in children and adolescents under the age of 18.

Fluorescein Sodium 100 mg/ml, Solution for Injection can only be obtained on prescription from a doctor.

For further information on how Fluorescein Sodium 100 mg/ml, Solution for Injection is used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet available on the MHRA website.

How does Fluorescein Sodium 100 mg/ml, Solution for Injection work?
Fluorescein Sodium 100 mg/ml, Solution for Injection contains the active ingredient fluorescein sodium which works as a diagnostic stain. Fluorescein angiography is a test that allows the blood vessels in the back of the eye to be photographed as a fluorescent dye is injected into the bloodstream. This will assist a doctor in the diagnosis of diseases which affect these blood vessels, especially in elderly people and diabetics.
What benefits of Fluorescein Sodium 100 mg/ml, Solution for Injection have been shown in studies?
As fluorescein sodium is a well-known substance and has a well-established use, the applicant (Viken Pharma Limited) presented data from the scientific literature. The literature provided confirmed the efficacy and safety of fluorescein sodium indicated for fluorescein angiography of the ocular fundus.

What are the possible side effects from Fluorescein Sodium 100 mg/ml, Solution for Injection?
The most common side effect with Fluorescein Sodium 100 mg/ml, Solution for Injection (which may affect more than 1 in 10 people) is nausea.

The most common side effects with Fluorescein Sodium 100 mg/ml, Solution for Injection (which may affect up to 1 in 10 people) are vomiting, blackout (also known as syncope), redness and itching of the skin, discolouration (yellowing) of the skin and eyes, discolouration (yellowing) of the urine, abdominal discomfort, pain at the site of injection (If the product leaks into the tissue surrounding the site of the injection (extravasation), a painful inflammatory reaction could occur even leading to the death of tissue).

For the full list of all side effects reported with Fluorescein Sodium 100 mg/ml, Solution for Injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Fluorescein Sodium 100 mg/ml, Solution for Injection approved?
The use of Fluorescein Sodium 100 mg/ml, Solution for Injection for the approved indication is well-established. Literature data have been submitted to support this application. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Fluorescein Sodium 100 mg/ml, Solution for Injection outweigh the risks and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Fluorescein Sodium 100 mg/ml, Solution for Injection?
A risk management plan has been developed to ensure that Fluorescein Sodium 100 mg/ml, Solution for Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fluorescein Sodium 100 mg/ml, Solution for Injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Fluorescein Sodium 100 mg/ml, Solution for Injection
A Marketing Authorisation was granted in the UK on 21st October 2014.

The full PAR for Fluorescein Sodium 100 mg/ml, Solution for Injection follows this summary. For more information about treatment with Fluorescein Sodium 100 mg/ml, Solution for Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2015.
Fluorescein Sodium 100 mg/ml, Solution for Injection

PL 41349/0001

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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Viken Pharma Limited a Marketing Authorisation for the medicinal product Fluorescein Sodium 100 mg/ml, Solution for Injection (PL 41349/0001) on 21st October 2014. The product is a prescription-only medicine (POM) indicated for fluorescein angiography of the ocular fundus. This medicinal product is for diagnostic use only.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of a well-established use. Therefore the evidence provided to demonstrate the safety and efficacy of this product is bibliographic in nature, which is appropriate for applications of this type.

Fluorescein sodium is a fluorochrome and when exposed to blue light (465 to 490 nm) exhibits yellow-green fluorescence (520 to 530 nm). It is used in medicine as a diagnostic stain. The fluorescence exhibited under certain wavelengths of light makes it possible to detect pathological changes (angiography) in the retinal circulation (ocular fundus).

Bibliographic data on Fluorescein Sodium have been submitted to support this application. No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of a well-established use.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.
II QUALITY ASPECTS

II.1 Introduction

This application is submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

This product is a solution for injection and contains 100 mg/ml fluorescein sodium as an active ingredient. The pharmaceutical excipients present are sodium hydroxide (for pH adjustment) and Water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

Fluorescein Sodium 100 mg/ml, Solution for Injection is packed in a 5 ml type I colourless glass ampoule; 10 ampoules packed in outer carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Fluorescein sodium

Chemical name: -3,6 ' - dihydroxyspiro- [isobenzofuran-1 (3H), 9 ' [9H] xanthen] - 3-one-acid 2 (3-oxo-6-oxydo-3H-xanthén-9-yl) benzoic

Structure:

Molecular formula: C$_{20}$H$_{10}$Na$_2$O$_5$

Molecular weight: 332.3 g/mol

Appearance: Fluorescent dye soluble in alkaline solutions with a yellow perceptible green fluorescence.

Solubility: Fluorescein is an orange-red fine powder which is practically insoluble in water, soluble in hot ethanol (96 per cent) and dissolves in dilute solutions of alkali hydroxides.

Fluorescein is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product
   Pharmaceutical Development
   The objective of the development programme was to formulate a safe, efficacious, stable solution for injection containing 100 mg/ml fluorescein sodium.

Suitable pharmaceutical development data have been provided for this application.

   Manufacturing Process
   A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using one commercial scale batch and two pilot scale batches and has shown satisfactory results. This is acceptable.

   Finished Product Specification
   The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

   Stability of the product
   Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing.

   Based on the results, a shelf-life of 3 years before opening the ampoule with no special storage conditions has been set. After first opening, the product must be used immediately. These are satisfactory.

   Suitable post approval stability commitments have been provided to continue stability studies on batches of the finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
   No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

### III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

### III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

### III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended to replace existing products in UK market there will no increased exposure to the environment.

### III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

### IV CLINICAL ASPECTS

#### IV.1 Introduction
This application is made under Article 10(a) of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of a well-established use. Bibliographic data on fluorescein sodium have been submitted to support this application. No new clinical studies were conducted for this application and none are required. The applicant’s clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

#### IV.2 Pharmacokinetics

$T_{\text{max}}$ is immediate after intravenous injection and thereafter concentration declines rapidly (rapid drop within first 10 minutes).

After intravenous injection into the antecubital vein, the fluorescence appears in the retinal vessels within a few seconds [8 to 20 seconds or 7 to 14 seconds]. It is rapidly distributed and distributes well into the interstitial space; the volume of distribution has been estimated at 0.5L/Kg.

It is metabolised via glucuronidation in the liver and excreted mainly via the kidney. Fluorescein monoglucuronide is about 1/3 to 1/34 as fluorescent as, depending on the wavelength of excitation of the blue light.

Fluorescein and its metabolites are eliminated in bile and urine, but mainly via renal excretion. A renal clearance of 1.75 ml/min/kg and a hepatic clearance (due to conjugation) of 1.5 ml/min/kg have been estimated. After 24 hours, most fluorescein is eliminated, although it may be traced for about a week in the urine.

Eye’s Distribution:
Following a pre-filling phase (when pictures are taken before injection distribution in the eye can be divided into three phases, transit, recirculation and a late phase.

**Transit phase:** Following fluorescein injection, dye is first visualized in choroidal and optic nerve vessels (named choroidal flush, occurring about 10 seconds after injection). Immediately after the choroidal flush, the retinal circulation filling then begins. Once the dye is seen in the central retinal artery, the Fluorescein travels into the pre-capillary arterioles, the capillaries and the post capillary venules and then exits the eye through the central retinal vein (arterial, capillary and then venous parts of this phase). After 30 seconds the first pass of Fluorescein through the normal retinal and choroidal vascularization is completed.
**Recirculation phase:** This occurs as fluorescein becomes equally distributed throughout the blood and re-enters the eye; during which there is intermittent mild fluorescence. This is essentially complete approximately 3 minutes after injection and at 10 minutes, both retinal and choroidal circulations are generally devoid of Fluorescein. Early leakage usually occurs during this phase.

**Late phase:** This occurs during the elimination phase with removal of fluorescein from the circulation, during this time any late staining or residual leakage is seen and is complete within 20 to 30 minutes.

Both the systemic pharmacokinetics and the ocular pharmacokinetics of fluorescein sodium have been reasonably well-characterised from literature.

**IV.3 Pharmacodynamics**

Fluorescein exposed to blue light (465 to 490 nm) exhibits yellow-green fluorescence (520 to 530 nm). This fluorescence makes it possible to detect pathological changes in the retinal circulation.

Following an intravenous injection of fluorescein sodium in an aqueous solution, the unbound fraction of the fluorescein can be excited with a blue light flash from a fundus camera as it circulates through the ocular vasculature, and the yellowish green fluorescence of the dye is captured by the camera. In the fundus, the fluorescence of the dye demarcates the retinal and/or choroidal vasculature under observation, distinguishing it from adjacent areas/structures.

In addition, it can be noted that the molecular size of fluorescein prevents its passage through the tight endothelial junctions of retinal blood vessels and zonula occludens in the intact retinal pigment, while allowing for rapid diffusion in fluids compartments.

The mechanism of action of fluorescein depends on its well-known physicochemical properties and it is accepted as a good diagnostic agent for imaging of retinal circulation.

**IV.4 Clinical efficacy**

There are a number of published reviews in retinal pathologies like Age Related Maculare Degeneration (ARMD) and Diabetic Retinopathy (DR) where the literature suggests that fluorescein imaging is the diagnostic standard and is the basis of treatment. There are also publications for the use of fluorescein angiography (FA) in other ocular diseases such as uveitis, Behcet’s disease, Glaucoma and staphyloma but to a comparatively lesser extent.

The following evidence for its use as a diagnostic agent in ARMD were included:

- A retrospective review of 252 patients examined within the first month of symptoms of exudative AMD where FA was used to determine eligibility of patients for laser photocoagulation or photodynamic therapy.
- A retrospective study of 108 AMD patients where FA was used as the diagnostic agent.
- A retrospective study of 16 patients where FA was used to detect CNV
- FFA on a regular basis to monitor the course of prophylactic macular photocoagulation
- FA which was correlation with OCT findings in a study of classic CNV secondary to AMD (n=60)

The following evidence for its use as a diagnostic agent in DR were provided:
To compare fluorescein leakage with retinal thickness maps obtained by OCT in 30 patients of DR. It was concluded that FA leakage in the outer ETDRS fields correlates best with central thickness and retinal thickness topography by OCT.

To compare the ability of 4 retinal specialists to plan laser treatment with and without FA in 100 consecutive cases of CSME.

The results showed that for the observer as a group, the use of FA improved treatment planning accuracy from 49% to 54.5% (p=0.02); however there was a significant inter observer variation in performance (p<0.001). Treatment planning accuracy without and with FA was as follows: observer 1, 40.8% and 40.2%; observer 2, 49.8% and 72%; observer 3, 56% and 59.5% and observer 4, 49.2% and 46.4%. It was concluded that the use of FA improves the accuracy of treatment planning for CSME. The authors’ study supports the use of FA in laser treatment of patients with CSME.

The following evidence has been shown for its use as a diagnostic agent in other ocular conditions:

- For the utility of FA in patients with posterior uveitis
- For the use of FA to evaluate choroidal abnormalities in Behcet’s disease
- For the use of FA and HRt to characterise optic nerver head damages in primary open angle glaucoma and chronic primary angle closure glaucoma
- For the use of FA and ICG-A to characterise changes in the anterior segment in corneoscleral inflammation

The evidence of efficacy for use of FA as a diagnostic agent in ocular conditions is not typical of the evidence seen for a novel diagnostic agent. There are no typical studies characterising the diagnostic potential of FA as compared to other gold-standard techniques. However there is plenty of literature which suggests and has used FA as the gold-standard diagnostic technique in the diagnosis of ocular pathologies more specifically those that significantly affect retinal circulation. The literature in other pathologies affecting the anterior segment of the eye is not so convincing or compelling. However it is noted that the claimed indication is for ‘angiography of the ocular fundus’ which is supported by the literature evidence.

**IV.5 Clinical safety**

Post-marketing data from a similar medicinal product approved in France were supplied in addition to published safety data and PSUR. Safety is adequately reviewed in the clinical overview. The safety profile of fluorescein sodium is well-known.

Fatal allergic accidents are known to occur in approximately 1/200,000 examinations.

An international survey collected information from 260 clinics and 30 different countries on 594,687 angiographic procedures; the incidence of serious adverse drug reactions (ADRs) was of 1/18020, and that of fatal reactions, 1/49557. These ADRs included anaphylactic shock, cardiac arrest, myocardial infarction and shock with hypotension or respiratory distress.

A United States survey of 221 781 fluorescein angiograms reported frequency rates of 1/63 for a moderate ADR (urticaria, syncope, thrombophlebitis, pyrexia, tissue necrosis or nerve palsy) and 1/1900 for severe ADRs (respiratory or cardiac events or tonic-clonic seizures) and one death was reported (1/222000).

A recent retrospective survey of all ADRs to IV sodium fluorescein in patients undergoing FA between June 1998 and June 2004 was undertaken. The total number of fluorescein angiograms performed and the number of patients with ADRs were identified from the photographic department database and the...
flourescein ADR register. All the patients were dilated with 1% tropicamide and 2.5% phenylephrine eye drops prior to the procedure. The concentration of fluorescein was 10% and the volume injected 5 mL in most cases. A total of 11,898 Fluorescein angiograms were performed during the study period. There were 132 ADRs recorded collected from 66 female and 66 male patients. The most common ADRS were nausea and vomiting (See Table 2).

**TABLE 2: DIFFERENT TYPES OF ADVERSE DRUG REACTIONS (from Ref 40 Kwan et al)**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Types of adverse reactions</th>
<th>No of adverse reactions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Nausea</td>
<td>87 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>47 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>34 (0.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Faint</td>
<td>17 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Localized reaction</td>
<td>14 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>28 (0.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>Seizure</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic attack</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>0</td>
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</tbody>
</table>

In the period from 1st September 2002 to 27th January 2012, based on the PSUR of Fluocyn, it is seen that there were 15 individual case safety reports (ICSRs) including 11 serious and 4 non-serious events. Details of these 15 ICSRs are gathered, by system organ class, in the following Table 3.

**TABLE 3: DETAILS OF THE 15 INDIVIDUAL CASE SAFETY REPORTS BY SYSTEM ORGAN CLASS**
The safety profile for fluoroscein angiography has been well characterised. Taking in to consideration the nature and frequency of the reported adverse events, there are no significant safety concerns for fluoroscein angiography. The only serious event is anaphylaxis which is fortunately rare. However due to the fatal consequences of this event due care must be exercise in the administration of this product which includes availability of resuscitation equipment and expertise to handle anaphylaxis.

**Overall clinical conclusion**

The proposed formulation and the other formulations used in published studies are from different intravenous solutions of fluroscein sodium. This is acceptable as they are simple solutions for intravenous injections. The excipients in the proposed formulation are standard excipients and are not expected to alter significantly the pharmacokinetic and consequently the pharmacodynamic characteristics of the proposed formulation. It is also reasonable to expect that the formulations used in the published studies will also be similar and will be made of standard excipients. Therefore no concerns are being raised in this regard.

**IV.6 Risk Management Plan (RMP)**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluorescein Sodium 100 mg/ml, Solution for Injection.

**Summary of the safety concerns**

<table>
<thead>
<tr>
<th>Type of risks</th>
<th>Safety concerns</th>
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<tbody>
<tr>
<td>Important identified risks</td>
<td>• Severe hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>• Extravasation</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>• Drug interactions</td>
</tr>
<tr>
<td>Important missing information</td>
<td>• Exposure during pregnancy</td>
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<tr>
<td></td>
<td>• Use in paediatric patients</td>
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<tr>
<td></td>
<td>• Exposure in patients with renal or liver impairment</td>
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</table>
For all the above mentioned risks, routine risk minimisation measures will include information in the product information (both in SmPC and PIL); no additional risk minimisation activities have been proposed.

<table>
<thead>
<tr>
<th>Safety concerns</th>
<th>Routine risk minimisation activities</th>
<th>Additional risk minimisation activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypersensitivity reactions</td>
<td>Information in the Product Information (SPC and PIL)</td>
<td>None proposed</td>
</tr>
<tr>
<td>Extravasation</td>
<td>Information in the Product Information (SPC and PIL)</td>
<td>None proposed</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Information in the Product Information (SPC and PIL)</td>
<td>None proposed</td>
</tr>
<tr>
<td>Exposure during pregnancy</td>
<td>Information in the Product Information (SPC and PIL)</td>
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</tr>
<tr>
<td>Use in paediatric patients</td>
<td>Information in the Product Information (SPC and PIL)</td>
<td>None proposed</td>
</tr>
<tr>
<td>Exposure in patients with renal or liver impairment</td>
<td>Information in the Product Information (SPC and PIL)</td>
<td>None proposed</td>
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</table>

**IV.7 Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended.

**V USER CONSULTATION**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

**VI OVERALL CONCLUSION, BENEFIT-RISK ASSESSMENT AND RECOMMENDATION**

**QUALITY**
The important quality characteristics of Fluorescein Sodium 100 mg/ml, Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of fluorescein sodium are well-known, no additional data were required.

**CLINICAL**
No new clinical data were submitted and none were required for applications of this type.
The published literature supports the efficacy of this product in the proposed indication. The efficacy of fluorescein sodium is well-known. The presented evidence for well-established use of the active substance is sufficient.

The safety profiles of fluorescein sodium are well-known. The literature review identified no new or unexpected safety issues or concerns.

**PRODUCT LITERATURE**
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

**BENEFIT/RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with fluorescein sodium is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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