# BALVERSA™ (erdafitinib) – Ocular Toxicities: Overview, Screening and Management

**January 14, 2020 (V1.1)**

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

# Disclaimer:

Thank you for your interest in BALVERSA™ (erdafitinib). The following information is provided because of your specific unsolicited request and is not intended as an endorsement of any usage not contained in the Product Monograph.

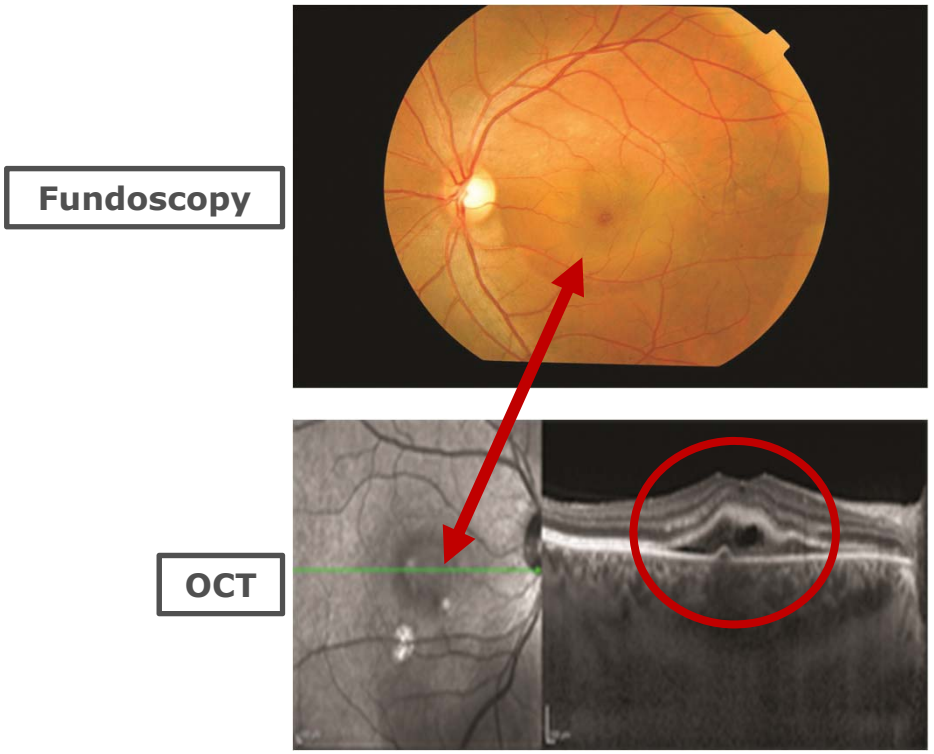
For complete information, please refer to the BALVERSA™ Product Monograph. For additional information, please see the full scientific summary accompanying these materials.†

† Please login to your JanssenMedicalInformation.ca account to view the scientific summary.

# Table of contents:

# Central Serous Retinopathy (CSR)[1-4]

- A condition in which fluid accumulates under the retina, causing a serous (fluid-filled) detachment of the retinal epithelium and vision loss
- Symptoms include blurry central vision, which often occurs in one eye
- Patients with CSR can show no symptoms, especially if the affected areas fall outside of the macula
- Detected and quantified with optical coherence tomography (OCT)
- Treatment is usually not necessary because most cases of CSR resolve without treatment after several weeks or months
- If retinal swelling persists for more than three or four months, or if an examination reveals early retinal degeneration, laser surgery may be helpful.




1. Francis et al., Ophthalmology. 2017 Dec;124(12):1788-1798.
2. Central serous chorioretinopathy. Retina Image Bank 2012; Image 2117. ©American Society of Retina Specialists Surgery PA. Retina Image Bank 2012; Image 1420. ©American Society of Retina Specialists.
3. Nicholson et al. *Surv Opthalmol.* 2013; 58(2):103-126.; 4. Canadian Ophthalmological Society: https://www.cos-sco.ca/vision-health-information/conditions-disorders-treatments/retinal-diseases/csr/ (Accessed: Jan 14, 2020)

# General Risk Factors for CSR

- One of the most frequent causes of vision reduction among middle-aged men

| Risk Factor | OR (95% CI) |
|---|---|
| Steroid usage | 4.29 (2.01-9.15) |
| Autoimmune disease | 3.44 (1.90-6.26) |
| Helicobacter pylori (H. pylori) infection | 3.12 (1.81-5.40) |
| Psychopharmacologic medication use | 2.69 (1.63-4.45) |
| Type-A behavior | 2.53 (1.08-5.96) |
| Sleeping disturbance | 1.90 (1.28-1.83) |
| Hypertension | 1.7 (1.28-2.25) |

Liu B, et al. *Retina*. 2016;36(1):9-19.

# General Treatment of CSR

## Acute CSR

- Typically self-limiting process

## Recovery

- Recovery of visual acuity typically occurs within 1-4 months
- Coincides with reattachment of the neurosensory retina

## Management

- Observation is the standard initial management to induce reattachment of the neurosensory retina
- Active management may be warranted if the duration is more than 4-6 months or a second episode follows a complete resolution of the first one
- Surgical interventions includes photodynamic therapy or subthreshold micropulse laser treatment

1. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.

# Incidence of Central Serous Retinopathy and Eye Disorders with Erdafitinib

**Proposed Mechanism[1]**

- FGFR signaling is thought to be involved in the maintenance, protection and repair of the retinal pigment epithelium for which inhibition could lead to CSR
- Erdafitinib also reacts with other tyrosine kinase receptors (RET, CSF1R, PDGFRA, FLT4, KIT, and VEGFR2) which may also contribute

As per the BALVERSA™ Product Monograph[2]:

- Ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect, were reported in patients receiving BALVERSA in clinical studies.
- CSR was observed in 25% of patients treated with BALVERSA in study BLC2001 at the 8 mg daily dose, with a median time to first onset of 50 days. The most commonly reported CSR events were chorioretinopathy (9%), retinal detachment (6%), and detachment of retinal pigment epithelium (6%).
- An abnormal Amsler grid test result was identified in the majority (70%) of patients who developed CSR.[1]
- Ocular disorders other than CSR occurred in 53% of patients, including dry eye (20%) and vision blurred (17%).[1]

1. Rosenthal et al. Biochem Biophys Res Commun. 2005 Nov 11;337(1):241-7.
2. BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

# Incidence of Central Serous Retinopathy and Eye Disorders with Erdafitinib – BLC2001

## Eye Disorders: Erdafitinib 8 mg Daily (N=99)*[1-2]

| Incidence | Onset | Dosing Modifications | Treatment Discontinuation |
|---|---|---|---|
| **CSR, n (%):**<br>**Any Grade:** 21 (21)<br>**Grade ≥3:** 3 (3)<br><br>**Non-CSR Ocular Events, n (%):**<br>**Any Grade:** 52 (52)<br>**Grade ≥3:** 5 (5) | **CSR, median onset:**<br>**Any Grade:** 53 days<br>**Grade ≥3:** 87 days<br><br>**Other Eye Disorders, median onset:**<br>**Any Grade:** 50 days<br>**Grade ≥3:** 162 days | **CSR, n (%):**<br>**Dose reduction:** 13 (13)<br>**Dose interruption:** 8 (8)<br><br>**Other Eye Disorders†, n (%):**<br>**Dose reduction:** 12 (12)<br>**Dose interruption:** 8 (8) | **CSR, n (%):**<br>**Discontinuation:** 3 (3)<br><br>**Other Eye Disorders†, n (%):**<br>**Discontinuation:** 3 (3) |

*Safety population included 87 patients previously treated with chemotherapy and an additional 12 chemotherapy-naïve patients who were ineligible for cisplatin-based therapy.

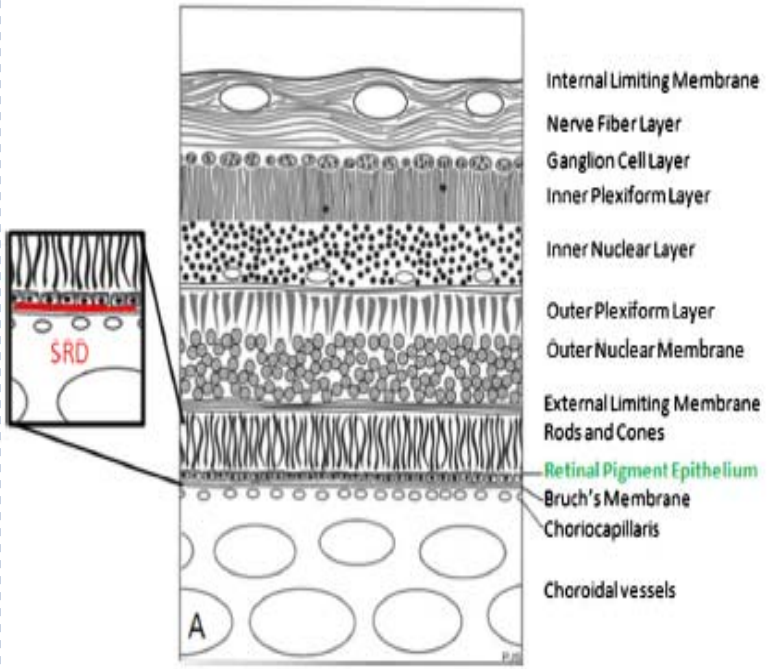
The BALVERSA™ Product Monograph describes safety results for the 87 patients previously treated with chemotherapy, therefore rates may differ.

†Other eye disorders occurring in ≥10% of patients included dry eye, blurred vision, conjunctivitis and increased lacrimation.

1. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.

# Screening Recommendation for CSR on Erdafitinib

- Prior to initiating BALVERSA, perform a **baseline ophthalmological exam** including an Amsler grid test, fundoscopy, visual acuity and, if available, an optical coherence tomography (OCT).[1]
- Examine patients **monthly** thereafter, using an Amsler grid test.[1]
- Patients should also be provided instructions to self-administer the Amsler grid test to detect visual abnormalities between physician visits.[1]
- The Amsler grid was used to screen for CSR in the BLC2001 study as described on Slide 13.[2]





1. BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.


Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

# Management Recommendations for Ocular Disorders on Erdafitinib

- If Amsler test is abnormal or if any visual abnormality is observed, follow the management guidelines in the BALVERSA Product Monograph as outlined in Table 3: Guideline for management of eye disorders with use of BALVERSA (see Slide 11).[1]
- To prevent and treat dry eyes, use artificial tear substitutes, hydrating or lubricating eye gels or ointments frequently, at least every 2 hours during waking hours. Severe treatment-related dry eye should be evaluated by an eye care professional (optometrist or ophthalmologist).[1]
- In clinical studies, CSR was **primarily managed by dose modification**, and led to dose interruptions and reductions in 9% and 14% of patients, respectively.[1]
- Three percent of patients discontinued BALVERSA due to CSR.[1]

1. BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

# Management of Eye Disorders (+ CSR) While on Erdafitinib

| Severity Grading | | BALVERSA™ Dose Management |
|---|---|---|
| Grade 1 | **Asymptomatic or mild symptoms; clinical or diagnostic observations only, or abnormal Amsler grid test.** | • Refer for an ophthalmologic examination (OE). If an OE cannot be performed within 7 days, withhold BALVERSA™ until an OE can be performed.<br>• If no evidence of drug-related corneal or retinal pathology on OE, continue at same dose level.<br>• If diagnosis from OE is keratitis or retinal abnormality (i.e.,CSR[a]/RPED[b]), withhold until resolution. If reversible in 4 weeks on OE, resume at next lower dose.<br>• Monitor for recurrence weekly for a month. Consider re-escalation if no recurrence. |
| Grade 2 | **Moderate; limiting age appropriate instrumental activities of daily living (ADL).** | • Immediately withhold and refer for an OE.<br>• If no drug-related corneal or retinal pathology on OE, withhold until resolution then resume at the next lower dose level.<br>• If OE diagnosis is keratitis or retinal abnormality (i.e. CSR/RPED), withhold until resolution.<br>• If resolved (complete resolution and asymptomatic) within 4 weeks on OE, resume at the next lower dose level.<br>• Monitor for recurrence every 1 to 2 weeks for a month. |
| Grade 3 | **Severe or medically significant but not immediate sight-threatening; limiting self-care ADL.** | • Immediately withhold until resolution.<br>• If resolved (complete resolution and asymptomatic) within 4 weeks, BALVERSA™ may be resumed at 2 dose levels lower.<br>• Monitor for recurrence every 1 to 2 weeks for a month.<br>• If recurs, consider permanent discontinuation. |
| Grade 4 | **Sight-threatening consequences; blindness (20/200 or worse).** | • Permanently discontinue |

CSR, central serous retinopathy; RPED, retinal pigment epithelium detachment.

BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

# Managing CSR: Dose Reduction Schedule

| Erdafitinib Dose Reduction Schedule | | | | | |
|---|---|---|---|---|---|
| **Dose** | **1st Dose Reduction** | **2nd Dose Reduction** | **3rd Dose Reduction** | **4th Dose Reduction** | **5th Dose Reduction** |
| **9 mg (three 3 mg tablets)** | 8 mg (two 4 mg tablets) | 6 mg (two 3 mg tablets) | 5 mg (one 5 mg tablet) | 4 mg (one 4 mg tablet) | **Stop** |
| **8 mg (two 4 mg tablets)** | 6 mg (two 3 mg tablets) | 5 mg (one 5 mg tablet) | 4 mg (one 4 mg tablet) | **Stop** | |

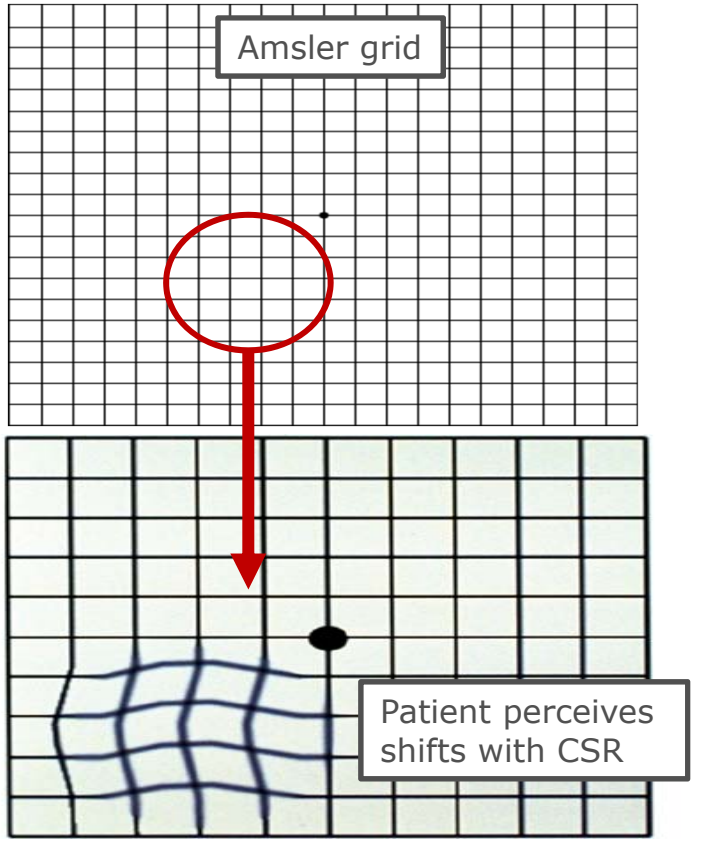
BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

# Screening of CSR in the BLC2001 Study Per Protocol

## Eye Disorders: Erdafitinib 8 mg Daily (N=99)*

- Utilization of the Amsler grid has a sensitivity and specificity of identifying CSR of 73% and 100%, respectively[1]
- The Amsler grid was used to screen for CSR on Day 1 of each new cycle beginning on Cycle 2
- Screening was performed in the office by treating physician or nurse (as directed by specific site instructions)
- Observations of wavy, broken or distorted lines, or a blurred/missing area of vision was considered positive
- Referral for a comprehensive ophthalmological exam was made within 7 days




*Safety population included 87 patients previously treated with chemotherapy and an additional 12 chemotherapy-naïve patients who were ineligible for cisplatin-based therapy. The BALVERSA™ Product Monograph describes safety results for the 87 patients previously treated with chemotherapy.

1. Klatt C, et al. *Ophthalmologe.* 2006;103(11):945-952.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.
3. American Society of Retina Specialists. https://www.asrs.org/patients/retinal-diseases/21/central-serous-chorioretinopathy. Accessed February 4, 2019.

# Management of CSR in the BLC2001 Study Per Protocol[1-3]

## Eye Disorders: Erdafitinib 8 mg Daily (N=99)*

- An abnormal Amsler grid result was noted during treatment for the majority (16 of 23; 70%) of subjects who developed CSR
- Twenty-four subjects (25%) had normal baseline assessments that shifted to abnormal at some point during therapy
- The change was reported as clinically significant for 11 subjects (12%), 7 of whom had events of CSR
- The majority of CSR events were Grade 1 or 2, with only 3 subjects on the 8-mg daily regimen having Grade 3 events
- Median time to first onset was 53 days for any grade event and 87 days for Grade >3 events

- Most subjects with CSR had their dose modified as a result of the event
- Majority were able to continue erdafitinib treatment following interruption or dose reduction
- At the time of data cutoff, CSR had resolved for 12 subjects; 11 subjects had ongoing events of which many had improved in severity and the majority were Grade 1
- No patient required surgical intervention

*Safety population included 87 patients previously treated with chemotherapy and an additional 12 chemotherapy-naïve patients who were ineligible for cisplatin-based therapy. The BALVERSA™ Product Monograph describes safety results for the 87 patients previously treated with chemotherapy.

1. Klatt C, et al. *Ophthalmologe.* 2006;103(11):945-952.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.
3. American Society of Retina Specialists. https://www.asrs.org/patients/retinal-diseases/21/central-serous-chorioretinopathy. Accessed February 4, 2019.

# Other Eye Disorders in the BLC2001 Study[1-2]

## Eye Disorders: Erdafitinib 8 mg Daily (N=99)*

| | |
|---|---|
| **Incidence** | • 55% of subjects were reported to have eye disorders of clinical importance<br>• Most common events (>10% of subjects)<br>  • Dry eye<br>  • Vision blurred<br>  • Conjunctivitis<br>  • Lacrimation increased |
| **Grade >3 Events** | • Six patients had eye disorders of Grade ≥3<br>  • Dry eye (n=1)<br>  • Cataract (n=2)<br>  • Keratitis (n=3)<br>  • Visual acuity reduced (n=1)<br>  • Corneal erosion (n=1)<br>• Median time to first onset was<br>  • Any Grade: 50 days<br>  • Grade ≥3: 162 days |
| **Treatment Discontinuation** | • Most of the 54 subjects continued erdafitinib treatment<br>• Some required dose interruption or reduction†<br>• Three subjects discontinued erdafitinib due to eye disorders; visual impairment, keratitis, visual acuity reduced (n=1 each) |

*Safety population included 87 patients previously treated with chemotherapy and an additional 12 chemotherapy-naïve patients who were ineligible for cisplatin-based therapy.
The BALVERSA™ Product Monograph describes safety results for the 87 patients previously treated with chemotherapy.


1. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.

# Management of Dry Eye in BLC2001 Study Per Protocol and the BALVERSA™ PM[1-3]

## General Considerations:

- Avoid unnecessary exposure to sunlight
- Use sunglasses in bright light

## Prophylactic Management:

- To prevent and treat dry eyes, use artificial tear substitutes, hydrating or lubricating eye gels or ointments frequently, at least every 2 hours during waking hours.[3]

## Reactive Management:

- Withhold for Grade 2-3 toxicity (or Grade 1 if OE cannot be performed in 7 days)[3]
- Artificial tears substitutes if not started, every 4 to 6 hours[1,2]
- Hydrating/lubricating eye gels and ointments[1,2]
- Refer severe treatment-related dry eye to an eye care professional (optometrist or ophthalmologist) for evaluation.[3]


1. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
2. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File.
3. BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

# Summary:

- Ocular disorders, including CSR/RPED resulting in visual field defect, were reported in patients receiving BALVERSA in clinical studies.
- In the phase 2 study, the majority of CSR events were Grade 1 or 2, with only 3 subjects on the 8 mg daily regimen having Grade 3 events.
- Median **time to first onset** was 53 days for any Grade event and 87 days for Grade >3 events.
- Prior to initiating BALVERSA, **perform a baseline ophthalmological exam** including an Amsler grid test, fundoscopy, visual acuity and, if available, an optical coherence tomography (OCT).
- Examine patients **monthly thereafter**, using an Amsler grid test.
- If Amsler test is abnormal or if any visual abnormality is observed, **follow the management guidelines** in Table 3 of the BALVERSA Product Monograph.
- In clinical studies, CSR was **primarily managed** by dose modification (interruption [9%], dose reduction [14%]).
- Majority were able to continue erdafitinib treatment following interruption or dose reduction (discontinuation rate was 3%).
- **To prevent and treat dry eyes**, use artificial tear substitutes, hydrating or lubricating eye gels or ointments frequently, at least every 2 hours during waking hours.
- Severe treatment-related dry eye should be evaluated by an eye care professional (optometrist or ophthalmologist).


1. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
2. BALVERSA™ (erdafitinib); the Canadian Product Monograph, October 25, 2019.

# Contact Information:

If you have any additional questions please contact

Janssen Medical Information

via

1-800-567-3331 (8:30-4:30 M-F EST)

www.janssenmedicalinformation.ca

(web-based conferencing is now available on request)

† Please login to your JanssenMedicalInformation.ca account to view the scientific summary.