TILLOTTS PHARMA
ZERIA GROUP

Rheinfelden, 23 July 2026

TO WHOM IT MAY CONCERN

Notification of an out of specification result in a single batch of of Fivasa (mesalazine) 400 mg modified-release tablets.

We would like to notify you about an out of specification (OOS 26-00029 Stab) result in dissolution in phosphate buffer pH 6.4 at t= 0months in an ongoing stability study of a single batch of Fivasa 400 mg FR modified release tablets. Fivasa is the French brand name for Octasa MR tablets (PL 36633/0002).

Octasa 400mg MR tablets rely on a pH-dependent coating to ensure the active ingredient is released only once they reach the colon, where the active ingredient is needed to treat inflammatory symptoms of ulcerative colitis. This gastro-resistant coating is intended to dissolve at a pH of 7 or above, ensuring release does not happen until the appropriate place in the gastrointestinal tract.

We recently informed MHRA of an out of specification finding with a single batch of Octasa 400mg MR tablets, where there was evidence of mesalazine release at pH 6.4 during ongoing stability studies. We report to you now a similar finding in a batch of Fivasa 400mg MR tablets manufactured for the French market, using the same process as Octasa 400mg MR tablets. It must be noted that the registered specification limits in France are less stringent than those registered in the UK and the batch is not out of specification in France.

Table 1 Details of the batch used for stability study

Finished product	Fivasa 400mg Tab FR
Finished product batch number	002813
Corresponding bulk batch number	82193G002
Manufacturing date	28.01.2026
Expiry date	12/2028
Source of drug substance	Cambrex
Bulk Manufacture	Haupt Pharma Wülfing, Gronau, DE
Packaging Site	Haupt Pharma Wülfing, Gronau, DE
Batch Certification	Haupt Pharma Wülfing, Gronau, DE
MAH	Tillotts Pharma FR
Stability study	Ongoing stability study (25°C / 60% RH and 30°C / 65% RH) (4558 AT400 ON 2026)

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The stability testing (t=0) of the above batch was performed in the frame of an on-going stability study at Haupt Pharma Wülfing, DE. The stability study was started with a batch of Fivasa 400mg Tab FR.
However, the stability study is representative for Octasa 400mg Tab UK.

Table 2 Stability study is representative also for Octasa 400mg Tab UK

Finished product	Octasa 400mg Tab UK
Bulk Manufacture	Haupt Pharma Wülfing, Gronau, DE
Packaging Site	Haupt Pharma Wülfing, Gronau, DE
Batch Certification	Haupt Pharma Wülfing, Gronau, DE
MAH	Tillotts Pharma UK (PL 36633/0002)

After first step of dissolution in acid stage, all tablets comply (no sign of disintegration or cracks) and one (1) out of six (6) tablets released API at buffer stage pH 6,4 (26%).

The specification requirements for Fivasa 400mg Tab FR are fulfilled. The stability specification for Octasa 400mg Tag UK are not fulfilled.

Octasa 400mg dissolution specification		**Stability results of batch #002813**
Parameter	**Stability requirements UK**	**T=0 months**
Dissolution 0.1M HCl (2 hours)	Resistant for 2 hours Cracks or disintegration (0/6)	P1: 0%, 0%, 0%, 0%, 0%, 0% ⇨ P1 level fulfilled
Dissolution pH 6.4 (1 hour)	P1 (n = 6): No individual value exceeds 10% (Q) of label claim dissolved. P2 (n = 6) The average value of the 12 dosage units (P1 + P2) is not more than 10% (Q) dissolved and no value is greater than 25% (Q+15%) dissolved P3 (n = 12): The average value of the 24 dosage units (P1+P2+P3) is not more than 10% dissolved and **no value is greater than 25%** (Q+15%) dissolved	P1: **26%**, 0%, 0%, 0%, 0%, 0% P2: 0%, 0%, 0%, 0%, 0%, 0% P3: 0%, 0%, 0%, 0%, 0%, 0% 0%, 0%, 0%, 0%, 0%, 0% ⇨ **OOS**

Dissolution pH 7.2 (1 hour)	P 1 (n=6): No value is <75% (Q+ 5%) of label claim dissolved. P2 (n=6): The average value of the 12 dosage units (P 1 + P 2) is equal or greater than 70% (Q) dissolved and no value is less than 55% (Q-15%) dissolved. P3 (n=12): The average value of the 24 dosage units (P1+P2+P3) is equal or greater than 70% (Q) dissolved and not more than 2 values are less than 55% (Q–15%) dissolved and no value is less than .45% (Q-25%)	P1: 97%, 95%, 97%, 95%, 99%, 97% P2: 96%, 98%, 97%, 96%, 94%, 93% P3: 95%, 97%, 97%, 95%, 96%, 94% 94%, 95%, 96%, 96%, 96%, 94% ⇨ P1 level fulfilled

Summary of Investigation for Fivasa 400mg Tab FR, batch 002813

The bulk manufacturing of Fivasa 400mg Tab FR are the same as for Octasa 400mg Tab UK.

The executed batch records of the bulk manufacturing and the packaging were reviewed, and the records did not indicate any deviations or unexpected events which could lead to the OOS result.

In addition, all IPCs and analytical release test results complied with the specification and did not show any unexpected results or trends.

Investigation to identify any lab error at the stability testing lab Haupt Pharma Wülfing, DE were performed, no lab error could be confirmed.

No crack or any signs of coating disintegration, that would allow the release of content, was visible during the stability testing.

The disintegration tests on all additional 6 tablets (Resistance test in 0.1M HCL (2h), Disintegration in Phosphate buffer pH 7.2) during the stability study testing comply with the specifications.

The other testing parameters of the stability specification are well within the requirements (t=0months). There is no trend for the dissolution results during stability studies running before for the manufacturing at Haupt Pharma Wülfing, DE.

47 batches of Octasa 400mg tablets were manufactured and packed at Haupt Pharma wolfing GmbH, DE and released to the UK market and are available on the market.

Complaint and adverse event reporting were reviewed for Octasa 400mg tablets UK over the last three years. No complaints or any adverse events were reported regarding lack of efficacy so far.

Health hazard assessment

Earlier release of Octasa 400 mg tablets at buffer stage pH 6.4 (but no release during resistance test in 0.1M HCL) does not present any increased risk in efficacy nor in safety for a patient. Mesalazine will still be released as intended and so the patient will receive the intended treatment, but release of the active may occur slightly earlier in the GI tract than intended. For context, other mesalazine drug product formulations on the UK market, with different release mechanisms release mesalazine at lower pH, confirming that this release mechanism is safe and efficacious. There is probably no major impact on efficacy because Cochrane meta-analysis had always concluded that there was no efficacy difference between the different formulations (meaning between earlier release formulations and later release formulations). Additionally, Ulcerative colitis is a chronic disease that needs multiple daily tablet administration - between 6 and 12 daily tablets. It is unlikely that around 25% earlier release would impact the efficacy of the treatment.

Potential Root Cause:

At the acid stage micro cracks might already be present, but due to their micro size could not be detected during the visual examination of each tablet according to the testing method. Such micro cracks might then lead to release of content at the next resistance stage (pH 6.4). Such micro cracks could be caused e.g. by mechanical stress during the manufacturing or packaging process and cannot be completely avoided.

Conclusion:

Based on the aforementioned evaluations there is no confirmed systematic quality issue on the product. The tablets which caused the release of mesalazine at resistance stage pH 6.4, are considered as an isolated event and is hence classified as a class III defect. This event is not expected to affect the efficacy or the safety profile of Octasa 400 mg tablets.

The OOS result for Fivasa 400mg Tab FR has no impact because the stability specification is fulfilled for France due to another method and specification limits. The batch can remain on the market during their shelf life.

Octasa 400 mg Tab UK batches can also remain on the market during their shelf life because no negative trend during stability studies or any confirmed systematic quality issue on the product.

Therefore, no further action is deemed needed.

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TWIMC Octasa 400mg Tabs Stab OOS 26-00029 Stab UK

Final Audit Report 2026-07-23

Created:	2026-07-23
By:	Friederike Rathing (friederike.rathing@tillotts.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAaqNzONXsSbUxA2y5fbQBUeOw2fr369tY

"TWIMC Octasa 400mg Tabs Stab OOS 26-00029 Stab UK" History

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