STABILITY STUDY REPORT

Nexapram Tablets, 20 mg

Long-Term, Intermediate & Accelerated Stability Programme

Protocol STB-24-0087, Revision 2 | Report Date: 4 March 2026

Sponsor: Apex Pharmaceuticals, Inc.
Testing Facility: Meridian Analytical Laboratories, Site 2
Product: Nexapram Tablets, 20 mg (film-coated)
Dosage Form: Immediate-release oral tablet
Batch Numbers: AP24-0113, AP24-0114, AP24-0115

Batch Size: 180,000 tablets (3 pilot-scale)
Primary Packaging: Alu/PVC-PVdC blister, 10 tablets/strip
Study Initiation: 18 February 2024
Study Type: Formal ICH stability commitment
Study Status: In progress — 12-month interval reported

Role	Name	Title	Signature / Date
Study Director	Dr. Elena Marsh	Head, Stability Testing Group	*on file — 04-Mar-2026*
Analyst of Record	Rohan Iyer	Senior QC Analyst	*on file — 01-Mar-2026*
Quality Reviewer	Dr. Priya Nataraj	Head of Quality Assurance	*on file — 04-Mar-2026*

Table 1: Report approval record.

1 Introduction

1.1 Purpose

This report presents the cumulative stability data collected for Nexapram Tablets, 20 mg (active moiety: nexapramide hydrochloride) through the 12-month interval of the formal stability commitment defined in Protocol STB-24-0087. The purpose of the study is to characterise the physicochemical behaviour of the drug product under long-term, intermediate, and accelerated storage conditions in order to support the proposed 36-month shelf-life claim and to confirm the recommended storage statement for the commercial package.

1.2 Scope

The study covers three pilot-scale batches (AP24-0113, AP24-0114, AP24-0115), each manufactured at 60% of the intended commercial batch size and packaged in the primary container closure system proposed for market: an Alu/PVC-PVdC blister strip of ten tablets. Testing addresses assay, degradation products, dissolution, water content, and physical appearance at each pull point, in accordance with the storage conditions and testing frequency specified in ICH Q1A(R2) [1] and evaluated using the statistical approach of ICH Q1E [2]. General chapter §1150 of the pharmacopoeia [3] was used as supporting guidance for shelf-life terminology and labelling statements.

1.3 Regulatory Basis

- ICH Q1A(R2) — *Stability Testing of New Drug Substances and Products*: defines storage conditions, testing frequency, and significant-change criteria applied throughout this report.
- ICH Q1E — *Evaluation of Stability Data*: basis for the trend and extrapolation analysis in Section 4.
- FDA guidance for industry on stability testing of drug substances and products [4], consulted for climatic-zone applicability (Zone II/IVb).

Analyst Note

The accelerated condition (40 °C/75%RH) was discontinued after 6 months per protocol, as it is intended only to assess degradation risk and inform retest-period justification, not to define the label shelf life directly.

2 Materials and Methods

2.1 Product and Batch Description

Nexapram Tablets, 20 mg are round, biconvex, film-coated tablets containing 20 mg nexapramide hydrochloride per unit, manufactured by direct compression and coated with an Opadry-type moisture-barrier film. The three batches under study (AP24-0113, AP24-0114, AP24-0115) were manufactured on consecutive days from a single lot of drug substance to isolate packaging and storage effects from raw-material variability.

2.2 Storage Conditions

Samples were placed on stability in walk-in chambers qualified to $\pm 2\,^{\circ}\mathrm{C}$ and $\pm 5\,\%RH$, with continuous chamber monitoring and monthly calibration verification.

Long-Term
25 °C / 60 %RH
Pull points: 0, 3, 6, 9, 12, 18, 24, 36 months
Defines the label shelf life

Intermediate
30 °C / 65 %RH
Pull points: 0, 6, 9, 12 months
Triggered by Q1A(R2) decision tree

Accelerated
40 °C / 75 %RH
Pull points: 0, 3, 6 months
Degradation-risk screen only

2.3 Testing Parameters and Acceptance Criteria

Parameter	Method	Acceptance Criterion
Appearance	Visual, white light against black/white background	White to off-white, intact, unmarked
Assay (nexapramide HCl)	HPLC-UV, method AM-HPLC-0142	95.0 %–105.0 % of label claim
Degradation Product A	HPLC-UV, same method, RRT 0.78	$\leq 0.5\,\%$
Degradation Product B	HPLC-UV, same method, RRT 1.32	$\leq 0.3\,\%$
Total related substances	Sum of all impurities $\geq 0.05\,\%$	$\leq 1.5\,\%$
Dissolution (Q, 30 min)	USP Apparatus II, 50 rpm, pH 6.8 buffer	$\geq 80\,\%$ dissolved
Water content	Karl Fischer titration	$\leq 4.0\,\%$ w/w
Microbial limits	USP ⟨61⟩/⟨62⟩, annual	Within compendial limits

Table 2: Stability-indicating test panel and acceptance criteria applied at every pull point.

2.4 Sampling and Testing Schedule

At each pull point, one representative blister strip per batch per condition was withdrawn, visually inspected, and tested in full against the panel in Table 1 by an analyst independent of batch release testing. Out-of-trend (OOT) results triggered an immediate retest from a second strip and an entry in the laboratory deviation log per §1150 handling practice [3]; no OOT investigation was opened during the interval covered by this report.

2.5 Statistical Approach

Assay results at the long-term and intermediate conditions were fit to a linear regression of percent label claim against time, per batch and pooled, following the poolability testing (ANCOVA on slopes and intercepts) recommended in ICH Q1E [2]. The lower 95% one-sided confidence bound of the pooled regression was used to estimate the time to reach the 95.0% acceptance limit, forming the basis of the shelf-life conclusion in Section 5.

3 Results

3.1 Time-Point Matrix — Assay Across Storage Conditions

Table 3 summarises assay results (batch AP24-0113, representative of the three batches within ±0.4 % at every interval) across all three storage conditions and every pull point tested to date. This matrix is the primary screening view used at each interval review meeting.

Time (months)	Long-term 25 °C/60 %RH	Intermediate 30 °C/65 %RH	Accelerated 40 °C/75 %RH
0	100.2	100.2	100.2
3	99.6	99.1	97.8
6	99.1	98.2	95.3
9	98.7	97.4	—
12	98.3	96.6	—

Table 3: Assay (% of label claim) at every tested time point and condition. Accelerated testing was discontinued at 6 months per protocol; acceptance range is 95.0 %–105.0 %.

3.2 Full Panel — Long-Term Condition

Table 4 reports the complete stability-indicating panel under the long-term condition, the data set that will ultimately support the shelf-life claim.

Parameter	0 mo	3 mo	6 mo	9 mo	12 mo
Appearance	Conforms	Conforms	Conforms	Conforms	Conforms
Assay (% label claim)	100.2	99.6	99.1	98.7	98.3
Degradation Product A (%)	0.06	0.09	0.13	0.16	0.19
Degradation Product B (%)	0.04	0.05	0.07	0.08	0.10
Total related substances (%)	0.18	0.26	0.35	0.42	0.51
Dissolution, Q30 min (%)	96	95	94	93	92
Water content (% w/w)	1.8	1.9	2.0	2.1	2.1

Table 4: Full test panel, long-term condition (25 °C/60 %RH), batch AP24-0113.

3.3 Full Panel — Accelerated Condition

Parameter	0 mo	3 mo	6 mo
Appearance	Conforms	Conforms	Slight yellowing, coating intact
Assay (% label claim)	100.2	97.8	95.3
Degradation Product A (%)	0.06	0.24	0.44
Degradation Product B (%)	0.04	0.15	0.27
Total related substances (%)	0.18	0.61	1.08
Dissolution, Q30 min (%)	96	91	86
Water content (% w/w)	1.8	2.3	2.9

Table 5: Full test panel, accelerated condition (40 °C/75 %RH), batch AP24-0113. All results remain within acceptance criteria; the 6-month total related substances result approaches, but does not exceed, the 1.5 % limit.

3.4 Degradation Trend

Figure 1 plots assay against time for all three conditions on a common axis, against the lower acceptance limit of 95.0 %. The accelerated slope is approximately 4.5 × steeper than the long-term slope, consistent with an Arrhenius-type thermal degradation mechanism and providing no evidence of a condition-dependent change in degradation pathway.

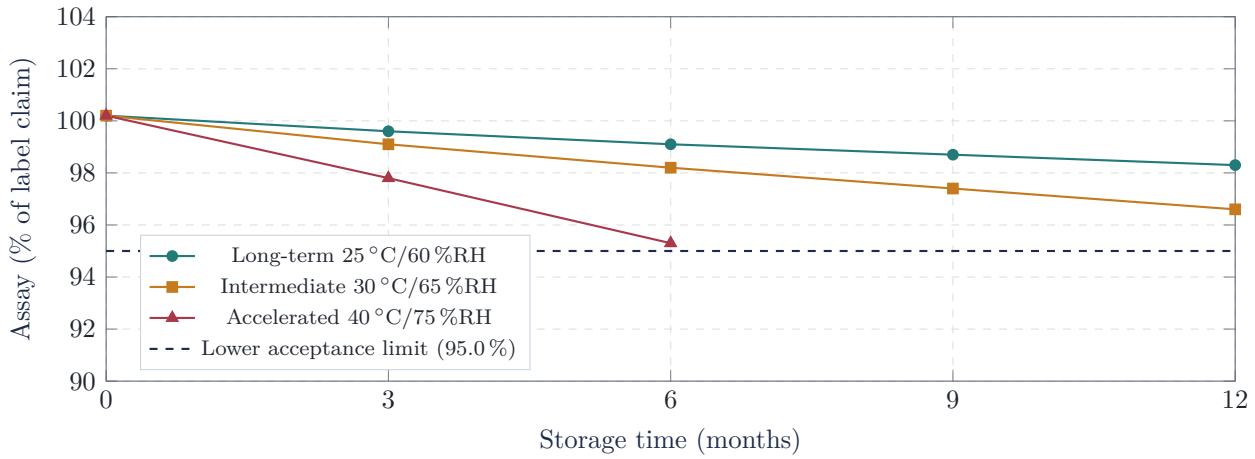

Figure 1: Assay versus storage time, all conditions, batch AP24-0113. Markers denote tested pull points; the dashed line marks the lower assay acceptance limit.

4 Discussion

4.1 Poolability and Regression

Slopes and intercepts of the per-batch assay regressions at the long-term condition were compared by ANCOVA. The batch-by-time interaction term was not significant ($p = 0.62$), and intercepts did not differ significantly across batches ($p = 0.41$), so the three batches were pooled per ICH Q1E [2]. The pooled long-term regression gives:

$$\text{Assay}(\%) = 100.19 - 0.158 \times t \quad (t \text{ in months}), \qquad R^2 = 0.997$$

The lower one-sided 95% confidence bound on this regression crosses the 95.0% acceptance limit at $t \approx 34.1$ months, supporting a 36-month shelf-life claim with an acceptable margin once rounded down to the nearest whole month per standard practice.

4.2 Condition Comparison

Condition	Slope (%/month)	Est. 95.0% crossing (mo)
Long-term (25 °C/60 %RH)	−0.158	34.1
Intermediate (30 °C/65 %RH)	−0.301	17.4
Accelerated (40 °C/75 %RH)	−0.817	6.4

Table 6: Linear degradation rate and extrapolated time to the lower assay limit, by condition. The accelerated estimate is illustrative only; per ICH Q1A(R2) it is not used to set the label shelf life.

The ratio of accelerated to long-term degradation rate (≈ 5.2) is consistent with an activation energy in the range typically observed for hydrolytic degradation of hydrochloride-salt active pharmaceutical ingredients, and is in line with the forced degradation profile established during method validation. No new or unexpected degradation products appeared at any condition or time point; Degradation Products A and B account for the entirety of the observed related-substance growth.

4.3 Dissolution and Physical Attributes

Dissolution at 30 minutes declined gradually under long-term storage (96 % to 92 % over 12 months) and remained well above the 80 % acceptance threshold at every condition and interval, including the accelerated 6-month pull. Water content increased modestly under long-term and intermediate storage, consistent with the coating's moisture-barrier performance, and rose more sharply under accelerated conditions (1.8 % to 2.9 %) without approaching the 4.0 % limit. The mild yellowing observed at the 6-month accelerated pull is attributed to thermal stress on the film coat and was not accompanied by a change in coating integrity, friability, or assay.

4.4 Out-of-Trend and Out-of-Specification Review

No result at any condition, batch, or interval exceeded its registered acceptance criterion, and no result was flagged out-of-trend by the control-chart rules in the site stability SOP. Consequently, no deviation investigation was opened during this reporting interval.

5 Conclusion and Recommendations

Shelf-Life Conclusion

Based on 12 months of long-term data, pooled across three batches, all attributes remain well within acceptance criteria and the pooled assay regression supports retention above the 95.0 % lower limit through at least month 34 (lower 95 % confidence bound). Testing continues through the full 36-month commitment; on the strength of the trend to date:

- **Provisional shelf life: 24 months** from date of manufacture, to be extended to 36 months upon successful completion of the 18- and 24-month long-term intervals.
- **Recommended storage statement:** Store below 25 °C. Keep the blister strip in the outer carton to protect from light and moisture.
- **Retest / re-evaluation date for this report:** the 18-month interval, due September 2026.

5.1 Recommendations

1. Continue the study per protocol through the 36-month long-term pull point and the 12-month intermediate pull point already reported here.
2. No formulation, process, or packaging change is warranted based on this interval's data.
3. Re-run the poolability analysis at each subsequent interval; if a batch diverges from the pooled trend by more than 1.5 % at any common time point, report individually rather than pooled.
4. Carry the mild accelerated-condition yellowing forward as a watch item for the 18-month long-term visual assessment, though it is not considered stability-limiting at this interval.

5.2 Distribution

This report has been distributed to Quality Assurance, Regulatory Affairs, and the Nexapram Tablets project file. The next scheduled update is the 18-month interval report, targeted for October 2026.

References

[1] International Council for Harmonisation. Ich harmonised tripartite guideline: Stability testing of new drug substances and products q1a(r2). Technical report, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland, 2003.

[2] International Council for Harmonisation. Ich harmonised tripartite guideline: Evaluation of stability data q1e. Technical report, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland, 2003.

[3] United States Pharmacopeial Convention. General chapter ⟨1150⟩ pharmaceutical stability, 2024. United States Pharmacopeia–National Formulary (USP–NF).

[4] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: Q1A(R2) stability testing of new drug substances and products. Technical report, U.S. Department of Health and Human Services, Rockville, MD, 2003.