CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216986Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 216986, Gadopiclenol injection
OPQ Integrated Quality Assessment (IQA)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	216986
Applicant Name	Guerbet LLC 821 Alexander Rd, Suite 204 Princeton, NJ 08540
Drug Product Name	(b) (4) (gadopiclenol) injection, for intravenous use
Dosage Form.	Solution
Proposed Strength(s)	0.5 mmol/mL
Route of Administration	Intravenous
Maximum Daily Dose	0.5 mmol/kg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated in adults and children aged 2 years and older for contrast enhanced MRI to (b) (4) lesions in the CNS of the body (head and neck, abdomen, pelvis and musculo-skeletal system).
Drug Product Description	A sterile, nonpyrogenic, clear, colorless to yellow aqueous solution of (gadopiclenol) injection for intravenous use with a pH range of 7 to (b) (4) and osmolality of 850 mOsm/kg water at 37^{0}C. Each mL contains 485.1 mg of gadopiclenol (equivalent to 0.5 mmol of gadopiclenol and 78.6 mg of gadolinium) and the following inactive ingredients, 0.404 mg tetxetan, 1.211 mg tromethamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment, if needed) in WFI.
Co-packaged product information	N/A
Device information:	N/A
Storage Temperature/ Conditions	25^{o}C (77^{0}F) and not to be frozen

Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joseph Leginus	Zhengfu Wang
	Drug Product/ Labeling	Dhanalakshmi (Dhana) Kasi	Danae Christodoulou
	Manufacturing (process/facilities)	Sureshbabu (Suresh) Dadiboyena	Kamal Tiwari
	Biopharmaceutics	N/A	N/A
	Microbiology	Ash Bekele	Yeissa Chabrier-Rosello
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh	
	ATL	Eldon E. Leutzinger	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 3 years at 25^0C (77^0F), excursions permitted to 15 – 30^0C (59 – 86^0F)

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Overall Rationale:

Summarizing over all components (drug substance, drug product, manufacturing and facilities, microbiology, and labeling), all deficiencies identified are resolved and there is

nothing left pending. All facilities have been approved based on the firm's history of inspections and manufacturing experience.

Summary of Assessments (Drug Substance):
The lion's share of the issues identified for the drug substance (drug substance review) comprise missing information on the **drug substance starting material** (b) (4) and for **Gadopiclenol drug substance**, its isomers (Iso 1, Iso 2, Iso 3, Iso 4) including their structures.

(b) (4) **All issues have been Resolved** and **nothing left pending** for drug substance (final review in panorama, 4/25/2022 with a recommendation of **APPROVAL**).

Summary of Assessments (Product Quality):
The issues for drug product fall into **3 main categories** (characterization, batch data and stability/specifications). Characterization focuses on what immediately becomes pertinent for a metal-ligand coordination entity – how well the metal cation stays bound to ligand, issues to which thermodynamic and kinetic stability (inertness) pertain, information requested of Guerbet.

Because of the large size of the thermodynamic stability constants, there are present extremely small levels of free Gd^{3+} ions in the aqueous solutions at low acidity. Hence, constants of log K 17 (or 1 x 10^{17}) and greater present difficulties in their determination. This is especially the case for constants of log 20 and up, generally found not measurable directly from acid-base titrations of the gadolinium ion and ligand, thus requiring competition studies with another ligand ($GdL + H_6Y = GdY + 6H^+$) to obtain reliable and accurate values for thermodynamic stability constants (and conditional stability constants). With increasing size of these constants, the decreasing levels of free Gd^{3+} result in insurmountable practical problems and measurement issues, resulting in larger measurement uncertainties to the extent where the determined values become meaningless.

Knowledge of the method of **determination is an important accompaniment to this physicochemical property (stability constant) for an understanding of its full significance**, not only in characterization but also in relation to pharmacological behavior, **hence the relevance of this requested information** (ATL).

Of all the other issues, those for which the appropriate information is necessary support product quality include batch data for the multiple fill volumes in filled vials and syringes. Also, within this category are requested data (raw HPLC chromatograms that

accompany the analytical methods for assay and impurity). **These are important for interpretation of the analytical test results and in the assessment of product quality**. Batch data in terms of three exhibit batches provides a "snapshot" of expected reproducibility of the production method, given continuity of quality of materials and continuity of suitability of the analytical methods in holding true to their intended purposes in quality controls. And for stability, there was incompleteness in the information in the original submission, including the photostability studies (assay), freeze-thaw studies and in-use stabilities. This information is critical for **understanding product sensitivity to any of the conditions proposed for storage and thus establish expiration dating**. The presence of the pyridine moiety heightens the importance of photostability. Because this moiety is built into the macrocycle ring, it brings photostability into the picture because of potential sensitivity of the polarized 'Gd-$N_{pyridine}$' bond (contiguous with pyridine's 1, 3, 5-conjugated triene system) (see Section 5, Additional Lifecycle Comments). Lesser important issues included extractable volume for the drug product filled in vials for all fill volumes. All these issues are **Resolved**, and nothing is left pending for drug product (final review 8/7/2022 in Panorama with a recommendation of **APPROVAL**).

Summary of Assessments (Manufacturing):
Here, it is process details that relate to manufacturing capability and cuts across those issues within the scope of method principles in drug substance and drug product CMC (reaction chemistry, analytical controls chemistry). The issues range from API lots used in manufacturing drug product to equipment (controls and compatibility) and operational principles, (b) (4) to proposed commercial scaling and batch records. **All issues have been Resolved** and nothing is left pending for manufacturing.

And all listed facilities for drug substance and drug product are approved based on the firm's inspection history and manufacturing experience.

There are two listed facilities, Liebel-Florsheim Company, LLC (Raleigh, NC, manufacturing, (b) (4) and Guerbet (Morihan, France, for manufacturing, final packaging, testing, release, and stability testing of drug substance). Final review is in Panorama 6/13/2022 with facility and process assessments of **ADEQUATE**.

Summary of Assessments (Microbiology):
Multiple deficiencies identified for microbiology in the original submission of the application ranged from ancillary (e.g., discrepancies in matching neck sizes in vials to stopper dimensions) to those more fundamental to establishment of product quality (dye ingress for integrity testing to (b) (4) to process validations to stability). (b) (4) A plethora of issues were identified within the area of process validation ((b) (4)), depyrogenation, endotoxin studies, (b) (4), etc. And there were issues regarding

various bioburdens and environmental monitoring. All are **Resolved** and **nothing remains pending** (final review in Panorama, 7/14/2022 with a recommendation of **APPROVAL**).

Summary of Assessments (Labeling - CMC):
Numerous issues were identified in the labeling and revisions made included those to product title, dosage forms and strengths, description, how supplied section and to the section for business name and location. For details on deficiencies and their revisions see the Labeling Review (Dhana Kasi, Ph.D., drug product reviewer). Labeling review 8/17/2022 in Panorama; with revisions, labeling is determined to be **ADEQUATE**.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Review & EI Statement - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

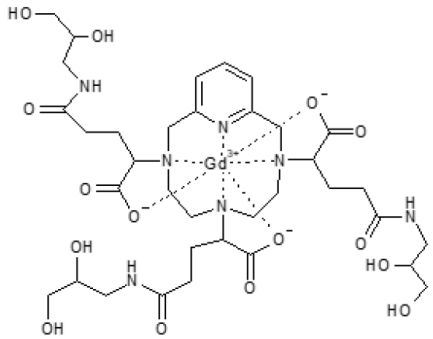
Additional Lifecycle Comments:

Qualified Supply Chain and Distribution Plan (ATL):
At the current time there are no known supply issues involving sources of gadolinium, a lanthanide (together with yttrium forming the rare earths). Although this has not always been the case within the family of rare earths (due to geopolitical issues), this aspect of the "complex product" complication does not impact Gadopiclenol.

However, the lack of these complexities belies any notion that there is anything a pushover for Gadopiclenol. **Rather, its "complexity" lies within the uniqueness of the ligand and how that affects Gd^{3+} binding and thereby stability and relaxivity,**

both of which play out in the pharmacological action of the drug (for a brief discussion and background, see Gadopiclenol, Notes on Product Complexity).

Gadopiclenol, Notes on Product Complexity (ATL):



The view seen in the above structure of Gadopiclenol, a **metal-ligand coordination entity**, is from top looking down vertically through Gd^{3+} (perpendicular to the plane of the page). From this topside view of the 3-dimensional structure, the most prominent feature in Gadopiclenol is the **pyridine moiety incorporated into the ring structure of the macrocycle** (***as opposed to being just a pendant group***) making this Gd-complex MRI agent unique compared to those that have thus far been FDA-approved.

Gd^{3+} (a lanthanide) prefers coordination numbers of 8 and 9, with the 9th being maximal. In its coordination compounds, after the ligand uses up 8 of Gd^{3+}'s 9 available coordination numbers, the 9th is typically occupied by a single water molecule. However, in Gadopiclenol there are only 7 sites in the ligand that can form bonds to Gd^{3+}. That leaves 2 of the maximal 9 coordination sites available in Gd^{3+} and invites **coordination of two exchangeable water molecules**, one each to fill the remaining 8th and 9th coordination sites in bonding. Both water molecules and ligand N-atoms/O-atoms are **directly bonded to the metal cation occupying together an inner sphere location in the complex**. However, the coordinated waters are bonded with lesser strengths than the ligand N,O's allowing them to be rapidly exchangeable.

Gd^{3+} is strongly electropositive, accounting for its attractivity to electronegative atoms (O, N) and its **propensity to form bonds with N,O-containing ligands** to form metal-ligand complexes. Theory has it that in bonding, the electron cloud of the $N_{pyridine}$ atom will be pulled toward Gd^{3+} (strongly electropositive Gd^{3+}) producing a distortion (a small cation polarizing a large anion, after Fajans') leaving the Gd-$N_{pyridine}$ bond polarized. Furthermore, being **incorporated into the ring structure of the macrocycle, rather than as a pendent group, brings the polarized 'Gd-$N_{pyridine}$' bond contiguous with pyridine's 1, 3, 5-conjugated triene system.** This in theory could influence the polarization of the Gd-$N_{pyridine}$ bond by resonance and potentially Gd^{3+}'s tightness within

the complex (subject to geometric constraints) and in turn potentially enhancing kinetic inertness to loss of Gd^{3+} from the complex.

The effect of the pyridine moiety as an integral part of the macrocycle ring may also have enhancing effects on thermodynamic stability, although a major contributor to thermodynamic stability in multidentate metal-ligand coordination entities is well-known to be the "Chelate Effect." In this context, there are only 7 sites in the ligand that can form bonds to Gd^{3+}, and hence only 7 chelate rings in Gadopiclenol, compared to 8 such rings with ligands that can form 8 bonds to Gd^{3+}. So, where in certain instances there is gain in kinetic inertness there may be some loss in thermodynamic stability, not uncommon with metal-ligand complexes.

Assessment of Chemical Type and Drug Classification Code (ATL):

As a result of the complexity of Gadopiclenol, the totality of the structural factors and the electronic effects of the Gd^{3+} - $N_{pyridine}$ bond working together provide a scientifically sound framework supporting a conclusion that the Gd-macrocycle in Gadopiclenol is indeed a discrete molecular entity and has the requisite 'stability' that, along with the exchangeable function of its inner sphere of coordinated waters, and other molecular characteristics influencing structure-activity, places it in the appropriate position of drug substance within the definition in 21 CFR 314.3.

Based on these considerations, Gadopiclenol is considered the substance furnishing *pharmacological activity or other direct effect in the diagnosis, cure, …of disease…"* (21 CFR 314.3), reference to MAPP 5018.2.

In summary,
What distinguishes Gadopiclenol from the panel of FDA-approved Gd-complexes of the macrocyclic type for MRI is the pyridine moiety covalently bonded internally (within the ring structure of the macrocycle, see the structure on previous page). And I am not aware of Gadopiclenol ever being marketed (without an FDA-approved NDA) as a drug in the United States, thus justifying a recommendation for NME based on MAPP 5018.2.

"*An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act or has been previously marketed as a drug in the United States.*"

Eldon Leutzinger

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	TRADENAME (gadopiclenol) injection, for intravenous use
Established name(s)	(gadopiclenol) (b) (4)	
Route(s) of administration	Injection for intravenous use.	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Injection: 0.5 mmol/mL of gadopiclenol in single-dose vials, single-dose prefilled syringes and pharmacy bulk packages (3)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

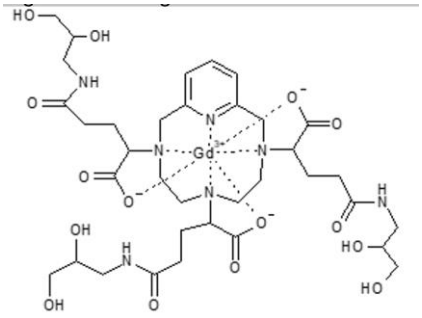
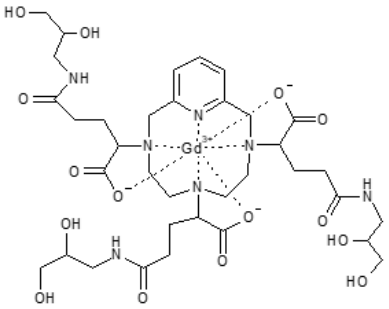
Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Section 3 (DOSAGE FORMS AND STRENGTHS		

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	Injection: TRADENAME is a clear, colorless to yellow aqueous solution at a concentration of 0.5 mmol/mL of gadopiclenol available as:
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		

Strength	Packaging
• 1.5 mmol/3 mL (0.5 mmol/mL) • 3.25 mmol/7.5 mL (0.5 mmol/mL) • 5 mmol/10 mL (0.5 mmol/mL) • 7.5 mmol/15 mL (0.5 mmol/mL)	Single-dose vials (glass)
• 3.25 mmol/7.5 mL (0.5 mmol/mL) • 5 mmol/10 mL (0.5 mmol/mL) • 7.5 mmol/15 mL (0.5 mmol/mL)	Single-dose prefilled syringes (plastic)
• 15 mmol/30 mL (0.5 mmol/mL) • 25 mmol/50 mL (0.5 mmol/mL) • 50 mmol/100 mL (0.5 mmol/mL)	Pharmacy bulk package (glass)

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	(b) (4) is a paramagnetic macrocyclic non-ionic complex of gadolinium (b) (4)	TRADENAME is a gadolinium-based contrast agent, which contains gadopiclenol, a paramagnetic macrocyclic non-ionic complex of gadolinium.
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	The chemical name for gadopiclenol is rac-[(2R,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-κ3N3,N6,N9-1(2,6)-pyridina-κN1-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-κ3O1,O1',O1'')(3−)]gadolinium.	The chemical name for gadopiclenol is rac-[(2R,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-κ3N3,N6,N9-1(2,6)-pyridina-κN1-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-κ3O1,O1',O1'')(3−)]gadolinium with a molecular weight of 970.11 g/mol and a molecular formula of C35H54GdN7O15
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	(b) (4) a molecular weight of 970.11 g/mol and a molecular formula of C35H54GdN7O15  (b) (4) is a sterile, nonpyrogenic, clear,	 TRADENAME is a sterile, nonpyrogenic, clear, colorless to yellow aqueous solution for intravenous use.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		

<table>
<tr>
<td>Other important chemical or physical properties (such as pKa or pH)</td>
<td>colorless to yellow aqueous solution.
Each mL contains 485.1 mg of gadopiclenol (b) (4) (equivalent to 0.5 mmol and 78.6 mg of gadolinium).
(b) (4) 0.404 mg tetraxetan, 1.211 mg trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment, if needed), and water for injection.
(b) (4)

The main physicochemical properties of (b) (4) are provided in Table 3.
Table 3: Physicochemical properties of ALTIVITY
<table>
<tr><th>Parameter</th><th>Value</th></tr>
<tr><td>Density at 20°C</td><td>1.211 g/cm^3</td></tr>
<tr><td>Mean viscosity at 20°C</td><td>12.6 mPa.s</td></tr>
<tr><td>Mean viscosity at 37°C</td><td>7.6 mPa.s</td></tr>
<tr><td>Osmolality at 37°C</td><td>850 mOsm/kg water</td></tr>
<tr><td>pH</td><td>7.0 – 7.8</td></tr>
</table>
(b) (4)</td>
<td>Each mL contains 485.1 mg of gadopiclenol (equivalent to 0.5 mmol of gadopiclenol and 78.6 mg of gadolinium) and the following inactive ingredients: 0.404 mg tetraxetan, 1.211 mg trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment, if needed), and water for injection.

The main physicochemical properties of TRADENAME are provided in Table 2.
Table 2. Physicochemical properties of TRADENAME
<table>
<tr><th>Parameter</th><th>Value</th></tr>
<tr><td>Density at 20°C</td><td>1.211 g/cm^3</td></tr>
<tr><td>Mean viscosity at 20°C</td><td>12.6 mPa.s</td></tr>
<tr><td>Mean viscosity at 37°C</td><td>7.6 mPa.s</td></tr>
<tr><td>Osmolality at 37°C</td><td>850 mOsm/kg water</td></tr>
<tr><td>pH</td><td>7.0 – 7.8</td></tr>
</table>
</td>
</tr>
</table>

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	
Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)		

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4)	
Strength(s) in metric system		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4)	TRADENAME is a clear, colorless to yellow aqueous solution supplied in the following presentations: (b) (4) Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature]. Do not freeze Pre-filled syringes.
	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].	
	(b) (4)	

Strength	Sale Unit	NDC
Single-Dose Vial (glass)		
1.5 mmol/3 mL (0.5 mmol/mL)	Carton of 1	67684-423-00
	Carton of 10	67684-423-01
3.25 mmol/7.5 mL (0.5 mmol/mL)	Carton of 1	67684-423-03
	Carton of 10	67684-423-04
5 mmol/10 mL (0.5 mmol/mL)	Carton of 1	67684-423-06
	Carton of 10	67684-423-07
7.5 mmol/15 mL (0.5 mmol/mL)	Carton of 1	67684-423-09
	Carton of 10	67684-423-10
Single-Dose Prefilled Syringe (plastic)		
[illegible]mmol/7.5 mL (0.5 mmol/mL)	Carton of 1	67684-423-40
	Carton of 10	67684-423-41
5 mmol/10 mL (0.5 mmol/mL)	Carton of 1	67684-423-43
	Carton of 10	67684-423-44
7.5 mmol/15 mL (0.5 mmol/mL)	Carton of 1	67684-423-46
	Carton of 10	67684-423-47
Pharmacy Bulk Package (glass)		
15 mmol/30 mL (0.5 mmol/mL)	Carton of 1	67684-423-12
	Carton of 25	67684-423-13
25 mmol/50 mL (0.5 mmol/mL)	Carton of 1	67684-423-15
	Carton of 25	67684-423-16
50 mmol/100 mL (0.05 mmol/mL)	Carton of 1	67684-423-18
	Carton of 6	67684-423-19
	Carton of 12	67684-423-20

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	See above	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.1 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Guerbet Manufactured by Liebel-Flarsheim Company LLC, 8800 Durant Road, Raleigh, North Carolina (NC) 27616-3104, USA Distributed by Guerbet LLC 214 Carnegie Center, Suite 300, Princeton, NJ 08540, USA	Manufactured by Liebel-Flarsheim Company LLC, 8800 Durant Road, Raleigh, North Carolina (NC) 27616-3104, USA Distributed by Guerbet LLC 214 Carnegie Center, Suite 300, Princeton, NJ 08540, USA Guerbet

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Medication Guide is included in the submission which contains the ingredients and manufacturer information from CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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(b) (4)

3.2 Carton Labeling

Assessment of Carton and Container Labeling: *Adequate*

Carton and container label will be changed for “intravenous use” instead of (b) (4) to match with PI.

Overall Assessment and Recommendation:

The applicant submitted separate labels for the pharmacy bulk package and vials, pre filled syringes in their original submission. The labels were combined together.

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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Danae Christodoulou

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	The drug product is a diagnostic agent for use in adults and children aged 2 years and older for contrast enhanced MRI to (b) (4) of lesions in the CNS and the Body (head and neck, abdomen, pelvis, and musculo-skeletal system)
NDA Number	216986
Assessment Cycle Number	1
Drug Product Name/ Strength	Gadopiclenol/G03277 Injection, (0.5 mmol/mL)
Route of Administration	Intravenous injection
Applicant Name	Guerbet Group
Therapeutic Classification/ OND Division	CDER/OND/OSM/Division of Imaging and Radiation Medicine
Manufacturing Site	Liebel-Flarsheim Company LLC, 8800 Durant Road, Raleigh NC 27616, USA FEI#: 1028892
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: Recommended for Approval

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001 (1), Original submission	01/21/2022
Seq 0008 (9), CMC IR response	04/01/2022
Seq 0009 (10), Labelling Filling Review issues	04/07/2022
Seq 0025 (26), IR response, Microbiology	06/09/2022
Seq 0027 (28), IR response, Microbiology	06/30/2022
Seq 0029 (30), IR response, Microbiology	07/08/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: None

Concise Description of Outstanding Issues: N/A
(List bullet points with key information and update as needed):

Supporting Documents:

- Type III DMF (b) (4) referenced for (b) (4) depyrogenation of the vial stoppers and the sterility assurance review of the DMF (D(b) (4)M17R01.doc, dated 05/20/2021).

- Type III DMF (b) (4) referenced regarding the (b) (4) process for the depyrogenation of syringe closure (plunger stoppers) and syringe tip caps, and the respective sterility assurance reviews of the DMF (D(b) (4)M40R01.doc dated 01/29/2020, and D(b) (4)M41R01.doc dated 03/08/2022).

Comparability Protocols: 1

- A comparability protocol was provided for (b) (4). The applicant proposes (b) (4).

S DRUG SUBSTANCE

The drug substance is tested for bioburden following USP <61> method (Limits: ≤ (b) (4) CFU/g for both total aerobic microorganisms and total yeast and mold), endotoxins per USP <85> method (limit of ≤ (b) (4) EU/mg). The drug substance is not reviewed for sterility assurance (b) (4)

Assessment: (Adequate)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Section 3.2.P.1, 2.P.1, Description and composition of the drug product (8-21-01818)

Description of drug product – The drug product (Gadopiclenol, 0.5 mmol/m) is a sterile, aqueous solution for intravenous injection packaged in the following ten presentations, including seven vial ((b) (4) clear glass) and three pre-filled syringes ((b) (4) plastic syringe).

Vial presentations (10 mL, 20 mL, 50 mL and 100 mL vials)

- 10-mL vial filled to 3 mL, single-dose
- 10-mL vial filled to 7.5 mL, single-dose
- 10-mL vial filled to 10 mL, single-dose
- 20-mL vial filled to 15 mL, single-dose
- **50-mL vial filled to 30 mL, Pharmacy bulk package
- **50-mL vial filled to 50 mL, Pharmacy bulk package
- **100-mL vial filled to 100 mL, Pharmacy bulk package

**Per the label (gadopiclenol-injection-track-change-uspi-pbp-april-6-2022), these are Pharmacy Bulk Packages, used as multiple-dose containers with “suitable transfer device” (not co-packed with the PBP presentation) to withdraw single doses to empty sterile syringes. Following withdrawal, each single dose should be used promptly. The label also instructs to penetrate the closure only once following aseptic procedures in aseptic work area such as laminar flow hood and leave the container in the aseptic work area. The contents of the Pharmacy Bulk Packages should be used within 24 hours after initial puncture, and any unused portions of the drug should be discarded.

The pre-filled syringe presentations (15 mL syringe)

- 15-mL syringe filled to 7.5 mL
- 15-mL syringe filled to 10 mL
- 15-mL syringe filled to 15 mL.

Drug product composition –The qualitative and quantitative composition of the drug product is described in the applicant table shown below.

Table 1: Composition of Gadopiclenol 0.5 mmol/mL Drug Product

Name of Ingredients	Unit Formula (for 1 mL solution)	Function	Reference to Standards
Drug substance:			
Gadopiclenol	485.1 mg[α]	Contrast agent in MRI	Internal monograph
Excipients:			
Tetraxetan (DOTA[δ])	0.404 mg	(b) (4)	USP-NF
Trometamol[γ]	1.211 mg		EP / USP-NF
Sodium hydroxide or/and hydrochloric acid	q.s. to pH (b) (4)	pH adjusting agent	EP / USP-NF
Water for injection(s)	q.s. to 1 mL	Solvent	EP / USP-NF

[α] *equivalent to 78.6 mg of gadolinium*

(b) (4)

Description of container closure system –A description of the primary container closure system along with the manufacturer's information is provided in the following applicant table modified from documents in section 3.2.P.7 (**Vials**: container-closure-system-vial, **syringes**: container-closure-system-syringe).

Description of the primary containers and closures

Container and closure	Manufacturer/Supplier	DMF No
(b) (4)		

(b) (4)

Comparison of the container and closure internal neck dimensions (modified from Section 3.2.P.7)

Vial size ((b) (4) glass)		Rubber Stopper		
Size	Internal neck diameter	Size	Plug diameter	Formulation
10 mL	17 ±0.669 mm	20 mm	12.95 ±0.15 mm	(b) (4)
20 mL	17 ±0.669 mm	20 mm		
50 mL	**29.0 mm**	32 mm	**23.2 ±0.1 mm**	
100 mL	**29.0 mm**	32 mm		

The Informational Requests (IRs numbered IR#1-IR#19), shown in italics throughout the review below, were sent to the applicant in the Agency's IR letter dated 09 May 2022. The applicant responses received on 09 June 2022 are summarized under each IR.

> ***IR#1.*** *We acknowledge the schematic diagrams of the vial sizes (10 mL, 20 mL, 50 mL, and 100 mL) and stopper sizes (20 mm and 32 mm) described in Section 3.2.P.7 for the primary container closure system of the commercial drug product. While we note that the 10 mL and 20 mL vials appear to have identical internal neck diameters and closed with identical 20 mm stoppers, the internal neck diameters of the 50 mL vials (16.27±0.64 mm) are vastly different from the 100 mL vials (29.0 mm). Therefore, provide a justification describing how the same 32 mm stoppers (with a plug diameter of 23.2±0.1 mm) tightly seal both the 50 mL and 100 mL vials. Additionally, if the dimensions (i.e, vial internal neck and internal stopper diameter) of the vial and stopper combinations for the 50 ml and 100 ml presentations are different, note that data from container closure integrity testing should also be provided to show that the proposed 50 ml vial with 32 mm stopper container closure system is able to maintain the sterility of the drug product.*

Applicant's response— Applicant confirmed that both the 50 mL and 100 mL vials have identical internal neck diameter (29.0 mm) and acknowledges that they previously provided a wrong "blueprint" for the 50 mL vial. In the IR response, the correct blueprint for the 50 mL vial was provided in Section 3.2.P.7. No further request will be made since the CCIT performed using the 100 mL vial represent the 50 mL vial, both vials are closed with the same 32 mm stopper.

Assessment: (Adequate)
The applicant provided acceptable description of the drug product and the primary container closure system. Based on the provided identical internal vial neck dimensions, the same "20 mm stoppers" can be used to close both 10 mL and 20 mL vials. Following the IR, the applicant confirmed that the 50 mL

and 100 mL vials have identical internal neck dimensions. Therefore, the same “32 mm stoppers” can be used to close both the 50 mL and 100 mL vials.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

[redacted]

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