الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidance for Paracetamol-Containing Liquid Dosage Forms Products Intended for Pediatrics

Draft

Date of publication	29 January 2020
Date of implementation	Refer to the implementation notice

This document is a draft SFDA guideline published for comments and suggestions purposes. It is, therefore, subject to alteration and modification and may not be referred to as SFDA guideline until approved by SFDA

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Drug Sector

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الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
Draft	Executive Directorate of Pharmacovigilance	29 January 2020	-

Implementation Notice[1]

Final version of this document is effective immediately for all new products seeking marketing authorization.

For registered products, companies encouraged to submit variation application to implement the requirement of the guideline.

After 18 months of publishing the final version of this document, the implementation is mandatory for all registered products.

[1] SFDA seeks companies' feedback regarding the implementation.

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1. INTRODUCTION

1.1. Objective

The Drug Sector in Saudi Food & Drug Authority (SFDA) has developed this document to promote safer use of products containing paracetamol by minimizing the potential of paracetamol overdosing and toxicity due to medication errors or accidental ingestion.

1.2. Background

Paracetamol is one of the most frequently administered medication to pediatrics worldwide. The current dosing instruction of registered paracetamol label mostly based on age not weight, which are imprecise and may result in inaccurate dosing due to marked variations in the weight of children of the same age. In 2015, a committee of experts led by SFDA has met to review the appropriate dosage labelling of paracetamol in children and infants.

The SFDA committee concluded a number of recommendations including:

1. Due to availability of different doses for the same child's age/weight, corrective action should be taken for paracetamol dosage labelling, based on child's weight to avoid sub-therapeutic dosing.
2. Ensuring the availability of a precise measuring device packaged within all marketed products.
3. Investigate dosage labelling for all paracetamol products that available in the market.

1.3. Scope

To provide applicants with guidance on the requirements necessary to receive marketing authorization for over the counter (OTC) oral liquid dosage forms containing paracetamol apply to both single-ingredient and combination-ingredient products for pediatric under 12 years of age.

1.4.Related Guidelines

This document should be read in conjunction with the following Drug Sector documents:

- The GCC Guidance for presenting the SPC, PIL and Labeling Information.
- Guidance for Graphic Design of Medication Packaging.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

In Saudi Arabia, paracetamol is available in several dosage forms and concentrations including:

2.1.Strengths

- Paracetamol 120mg/5ml
- Paracetamol 125mg/5ml
- Paracetamol 160mg/5ml
- Paracetamol 100mg/ml

2.2.Pharmaceutical Forms

Oral liquid formulation such as solutions, suspensions, syrup, drops and elixir.

3. REQUIREMENTS

3.1.Patient Information Leaflet (PIL)

In addition to the GCC Guidance for presenting the SPC, PIL and Labeling Information and the guidance for Graphic Design of Medication Packaging, the followings are special considerations for products containing paracetamol as OTC Products:

3.1.1. Therapeutic Indications

To relieve mild to moderate pain and to reduce fever in many conditions including headache, toothache, teething, feverishness, colds and influenza and following vaccination.

3.1.2. Dosage Direction for Children Under 12 Years

The dose should be weight-related dosing in the label instructions. If the weight of child's is unknown, the age related dosing is provided (Table 1 and 2).

Table 1: Dosage for children <12 years of age: 25 mg/ml; 24 mg/ml; 32 mg/ml paracetamol liquid

Age (Years)	**Body weight (kg)**	**Maximum Single dose**				**Maximum daily dose**			
		mg	25 mg/ml	24 mg/ml	32 mg/ml	mg	25 mg/ml	24 mg/ml	32 mg/ml
2-3	11.0-15.9	160	6.4 ml	6.6 ml	5 ml	800	32 ml	33.3 ml	25 ml
4-5	16.0-21.9	240	9.6 ml	10 ml	7.5 ml	1200	48 ml	50 ml	37.5 ml
6-8	22.0-26.9	320	12.8 ml	13.3 ml	10 ml	1600	64 ml	66.6 ml	50 ml
9-10	27.0-31.9	400	16 ml	16.6 ml	12.5 ml	2000	80 ml	83.3 ml	62.5 ml
11 to under 12	32.0-43.9	480	19.2 ml	20 ml	15 ml	2400	96 ml	100 ml	75 ml
Age (months)	**Body weight (kg)**	**Maximum Single dose**				**Maximum daily dose**			
		mg	25 mg/ml	24 mg/ml	32 mg/ml	mg	25 mg/ml	24 mg/ml	32 mg/ml
0-3	2.7-5.4	40	1.6 ml	1.6 ml	1.25 ml	200	8 ml	8.3 ml	6.25 ml
4-11	5.5-7.9	80	3.2 ml	3.3 ml	2.5 ml	400	16 ml	16.6 ml	12.5 ml
12-23	8.0-10.9	120	4.8 ml	5 ml	3.75 ml	600	24 ml	25 ml	18.75 ml

To minimize dosing errors, paracetamol oral drops solution of 100 mg/ml concentration should not be concurrently labeled for both infants (<2 years) and children (≥2 years). Thus, clear statement of "this product for infants under 2 years" should be available.

Table 2: Dosage of children under 2 years,: 100 mg/ml Paracetamol oral drops

Age (Months)	**Body weight (kg)**	**Maximum Single dose**		**Maximum daily dose**	
		mg	100 mg/ml	mg	100 mg/ml
0-3	2.7 - 5.4	40	0.4 ml	200	2 ml
4-11	5.5-7.9	80	0.8 ml	400	4 ml
12-23	8.0-10.9	120	1.2 ml	600	6 ml

3.1.3. Special considerations

The PIL should include the following:

- "Seek medical advice before giving to preterm neonate or term neonates <10 days".
- "Repeat 4 – 6 hourly up to 5 times per day if required. No more than 5 doses in any 24-hour period."
- For **25 mg/ml; 24 mg/ml; 32 mg/ml**: "Should not be used for more than 5 days for children ≥2 years and 3 days for infants (<2 years) except on medical advice."
- For **100mg/ml**: "Should not be used for more than 3 days at a time except on medical advice."
- "Should not be used with other paracetamol-containing products."
- The recommended single dose and maximum daily dose in ml, as well as the dosing interval for the product. Maximum daily dose may be expressed as: "Do not take more than ml or doses in 24 hours".
- Instructions specific for liquid dosage form, i.e. should not include all dosage forms of paracetamol in one PIL such as (tablet or suppositories,).

3.1.4. Warnings

- Under section 2 "Before you take or use the product": Liver warning: (should be bold font type): "This product contains paracetamol. Maximum daily dose is (XX ml) in 24 hours. Severe or possibly fatal liver damage may occur if you take more than the recommended dose in 24 hours or with other drugs containing paracetamol."
- "DO NOT USE with other drugs containing paracetamol. If you are not sure whether a drug contains paracetamol, ask a doctor or pharmacist."

3.2. Outer and Immediate Packaging

In addition to The GCC Guidance for Presenting the SPC, PIL, and Labeling Information, and SFDA Guidance for Graphic Design of Medication Packaging, the followings are special considerations for products containing paracetamol as OTC Products:

The quantitative declaration of the medicinal ingredients (paracetamol) on any panel of the immediate and outer packaging should be prominently displayed and should be further identified by the therapeutic class or indication “paracetamol (analgesic/antipyretic) 32 mg/ml”.

Concentration of paracetamol should appear in bold font type, clear font size and in black text with a white background in the middle of the label.

The immediate and outer packaging should contains the below warning:

- DO NOT USE with other drugs containing paracetamol. If you are not sure whether a drug contains paracetamol, ask a doctor or pharmacist.
- DO NOT USE if you are allergic to paracetamol or any other ingredient in this product
- For oral suspensions, shake the bottle well before use.

It is recommended that age group which the medicine is intended for should be declared in the outer packaging, pictures of children could help highlight medicines, which are suitable for children. Where children are used, they should appear to be in the age range that the medicine is intended for.

3.3. Pack Size and Container

Packaging should be standard child-resistant to prevent or delay pediatrics from opening bottles, giving caregivers reasonable time to intervene.

3.4. Combination

Marketing authorization holder should apply outside of the labelling standard if they wish to combine paracetamol with medicinal ingredient(s) such as sedative, antitussive,

antihistamine. Please note that all labelling requirements for paracetamol is also applies to products combining paracetamol with any other medicinal ingredient.

The statement: “this product Contains paracetamol and other Ingredients” should appear in bold font type and clear font size in the top right corner of the label. In addition, the text for “this product contains paracetamol” should appear in red with a white background.

- For small package sized products: Consideration will be given for products with small package size. However, the text for “Contains paracetamol” should appear prominently in bold font type in red with a white background in the top right corner of the label.

3.5.Delivery Device

For liquid formulations, it is required that an appropriate dosing device be provided and the following statement should be included with the directions for use: “Use only the measuring device provided”.

The dose information should be expressed in units of measure that correspond to the calibration of the dose delivery device, and include instructions that are consistent with the measuring device.

REFERENCE:

Health Canada Revised Guidance Document: Acetaminophen Labelling Standard. September 2016.